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ORIGINAL ARTICLES

PRACTICAL APPLICATIONS AND USES OF THE SCHICK TEST*

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THE subject of diphtheria in many of its aspects is thoroughly familiar to the medical profession at the present time, but it may not be generally realized that in spite of the modern methods of combating this disease, it is still quite active and prevalent throughout the world. The mortality in New York City alone has been about 1,400 cases each year for the first past five years; the morbidity about ten times as great. For the United States the calculated yearly mortality is from 20,000 to 22,000 and the morbidity from 150,000 to 200,000 cases. In pre-antitoxin days the mortality from diphtheria was 70 to 75 per cent. With the introduction of antitoxin in 1894, the mortality was gradually reduced to 10 per cent, where it has remained more or less stationary.

The above are striking figures when we consider that we have at our disposal in diphtheria antitoxin a remedial agent which would cure every case if applied early enough in the course of the disease. The fact remains, however, that for the past eight to ten years the number of fatal cases has remained more or less constant. This persistent and relatively high mortality can only be accounted for by the delayed application for treatment on the part of the patient, the delayed recognition of the disease on the part of the physician, or by both of these factors.

The more recent investigations in the control of diphtheria have shown us the great importance of the Schick test by means of which we can recognize very definitely every person who is susceptible to diphtheria. In conjunction with the Schick test it has been found that the vast majority of susceptible individuals can be actively immunized for a number of years and possibly for life by means of injections of toxin-antitoxin. We realize fully that it will be a ques-

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tion of years before there will be a universal application of these measures, but it is a work well worth while and will repay the effort.

In 1913 Schick[1] published the results of his investigations in which he stated that by means of a simple clinical test we could determine whether a person is susceptible to diphtheria or not. The test consists in the injection of a small amount of diphtheria toxin, properly diluted, into the skin of the forearm. We began using the test at the Willard Parker Hospital soon after his publication appeared. After seven years of intensive studies with this reaction we have come to the conclusion that the test is one of the most valuable and accurate clinical procedures at our disposal today.

I. FACTORS INFLUENCING THE RELIABILITY OF THE SCHICK TEST

The reliability of the results obtained with the Schick test, however, depends upon three important factors, which have to be carefully observed:

1. The toxin that is used for the test should be of standard strength.
2. The technic in making the intradermal injections must be correct.
3. The interpretation of the reactions must be accurate.

The toxin used in the test must be of standard strength. The dilution must not be so weak that the individual who should give a positive reaction will give a negative reaction, and it should not be so strong that a local area of severe necrosis will develop at the site of the injection. Schick determined that the amount of toxin for the test should be 1/50 of a minimum lethal dose for the guinea pig, in 0.1 c.c. of normal saline. We prefer 1/50 of an M.L.D. in 0.2 c.c. of saline, an amount which is more easily handled, and will show a small definite wheal-like swelling in the skin after the injection. The positive reactions noted in susceptible individuals with this dilution of toxin are not apt to be as severe and persistent as those noted with the more concentrated dilutions.

The toxin can now be obtained in a convenient outfit devised by me and supplied by the Research Laboratory. It consists of a small glass capillary tube containing the undiluted toxin, a small rubber bulb for expelling the toxin and a 10 c.c. bottle of saline in which the toxin is to be diluted before use. The toxin remains good for six months if kept in the cold undiluted. After dilution it should not be used later than twenty-four hours. One outfit is sufficient for about 35 tests. Similar outfits are supplied by several commercial laboratories. I have found after testing some of these commercial preparations, that unfortunately a number of them were below standard strength. These results have been communicated to the laboratories, and I have no doubt that the strength of the toxin in these preparations will be brought up to the standard.

The outfit supplied by the New York State Department of Health is good, but is not fool-proof. In this outfit there is a small vial of toxin from which with a graduated glass pipette a definite amount is withdrawn and diluted with the saline supplied in another vial. One physician emptied the entire contents of the toxin vial into the saline, and tested some 200 children. About 80 of these children had severe sloughing reactions as a result of the concentrated dilution of the toxin which was injected.

When we make the tests with a standard and carefully prepared dilution of the toxin, our results show that the test is perfectly harmless. The informa-

tion obtained is of extreme value because of the great accuracy of the Schick reaction. Of 2200 scarlet fever patients who gave negative reactions on admission to the Willard Parker Hospital, not one developed an undoubted clinical diphtheria. These children had received no antitoxin, were exposed to cases of diphtheria in neighboring beds and moreover some 20 to 25 per cent showed by culture that they were carriers of virulent bacilli. The fact that all of the 2200 proved immune to the disease is a striking corroboration of the accuracy of the Schick test.

The technic of the test is of great importance. The reaction is a local phenomenon and has to be visible to the eye. The test fluid, therefore, must be injected *intradermally* and not subcutaneously. A good syringe and a fine needle are necessary. A 1.0 c.c. Record syringe and a 26 gauge ¼ inch steel needle are probably best for this purpose. An ordinary hypodermic syringe will answer, but the needle should be finer than the ones that are generally used with such syringes. One must be careful to sterilize the syringe and needle by boiling, or with alcohol. If alcohol is used it must be rinsed out of the syringe with some of the diluted toxin and the rinsings discarded before making the tests. To make the test, inject 0.2 c.c. of the unheated and properly diluted toxin intradermally on the flexor surface of the right forearm about 2.5 inches below the bend of the elbow, and a similar amount of the heated diluted toxin used for control as described below in the left forearm. It is a good plan always to use the *right forearm* for the test and the *left forearm* for the control, as one will then be able to know exactly where to look for the reactions and how to interpret them.

The correct interpretation of the reactions is also of utmost importance. A *positive* reaction indicates that the child is susceptible to diphtheria; a negative reaction that he is immune to that disease. If a person is susceptible to diphtheria there will appear at the site of injection within 24 to 36 hours a definite well circumscribed area of redness about the size of a five cent piece, which gradually becomes more marked within the next two or three days. The reaction reaches its height on the fourth or fifth day. It persists for a week or longer, depending upon the intensity of the reaction, and leaves on fading a brownish area of pigmentation, which shows at first definite scaling. The pigmented area gradually fades, but may still be seen in some individuals even as late as three or four months. If a person is immune to diphtheria he shows a *negative* Schick reaction, the skin at the site of the test remaining unchanged. It has been found that if an individual has 1/30 of a unit of antitoxin or more per c.c. of serum, he will give a negative reaction. The reading of the reactions in children under 5 years of age is quite simple, as the reactions at this age are mostly positive or negative. In older children, however, and especially in adults, one meets with so-called *pseudonegative* reactions which make the reading more difficult. This reaction is found in immune individuals and must be carefully distinguished from the positive reaction. The pseudonegative reaction is produced by the autolyzed protein of the diphtheria bacillus, which is also present in the test fluid. This reaction is of the nature of an anaphylactic reaction. It appears much earlier than the positive reaction, is well marked at the end of eighteen hours and reaches its height at the end of twenty-four hours. At the

end of four days in a majority of the pseudonegative reactions most of the redness and the induration has faded away and there is left behind only a small irregular area of pigmentation, which may occasionally show a slight central scaling. These reactions vary in intensity, however, the degree depending upon the susceptibility of the individual to the autolyzed protein. Some of the pseudonegative reactions are very marked and may show even at the end of four days a well defined area of reddish brown pigmentation. The pseudonegative reaction, can, however, be accurately identified and distinguished from the positive Schick reaction by making a control test[3] on the left forearm with toxin which has been heated to 75° C. for ten minutes. The heating destroys the toxin, but does not affect the autolyzed protein. An individual who gives a *pseudonegative reaction* will show *similar reactions* in the *test* and in the *control*. An individual who gives a *positive reaction* will show an area of *typical redness* at the site of the *test*, which is always done on the right forearm, and *no reaction* at the site of the *control* on the left forearm. It is best to make a preliminary reading at the end of 48 hours and a final definite reading at the end of 96 hours. At the end of four days the positive reactions will be at their height, while the majority of pseudonegative reactions will have faded almost completely. The control test with *heated toxin* is most valuable, therefore, in positively identifying the character of the reactions.

A small proportion of susceptible individuals have a *pseudopositive* or *combined* reaction. This reaction represents a combination of both the positive and the pseudoreaction, and is identified at the end of 96 hours by a well defined positive reaction at the site of the test on the right forearm and a partly faded pseudoreaction at the site of the control on the left forearm.

The importance of identifying the pseudonegative reaction is evident from the fact that among adults there occur two or three times as many pseudonegative as positive reactions.

II. ACTIVE IMMUNIZATION OF INFANTS AGAINST DIPHTHERIA

In the newborn we find only about 15 per cent of positive Schick reactions. This number corresponds with the number of mothers who give positive reactions. The other infants are temporarily immune. This immunity is derived from the mother and is generally lost after the first six to nine months of life. Most of the children by the time they complete the first year of life give a positive reaction. This explains the great morbidity and mortality from diphtheria between the ages of one and five years. Over 80 per cent of deaths from diphtheria occur under five years of age.

In view of this very high morbidity and mortality in children under five years of age we[4] have urged that *every child* from six months to two years of age should receive the active immunization with toxin-antitoxin. This procedure is especially important as most of the children lose their maternal immunity when they reach the age of six to nine months. This susceptibility is readily shown by a positive Schick reaction, which is seen in such a large proportion of children at the age of one year. *In children under six months of age, toxin-antitoxin should not be used as it usually produces no immunization.* This is especially true in the first few months of life. After the child has passed its

second year of life the application of the Schick test is of great value in separating the children who are immune from those who are susceptible so that toxin-antitoxin injections may be given only to those who show a positive reaction.

III. MIXTURES OF TOXIN-ANTITOXIN USED FOR IMMUNIZATION

In 1913, at about the same time that Schick published his investigations, von Behring proposed a new method of active immunization with diphtheria toxin-antitoxin. The use of such mixtures was not new, but their application in human beings was taken up for the first time by this observer and his co-workers.

Von Behring gave no exact details as to the methods by which he prepared these mixtures.[5] His communications were therefore of little value to us at the Research Laboratory in guiding us in the preparation of the toxin-antitoxin. Of the different mixtures with which we worked, we finally came to the conclusion that a slightly toxic mixture gave the best results.[6] At first we had to determine these results by taking specimens of blood and examining them for their antitoxin content. This was tedious and unsatisfactory and we then began to use the Schick test in conjunction with the toxin-antitoxin immunization.[7] The work was thus greatly simplified. We were able to select the susceptible individuals, give them the toxin-antitoxin and subsequently prove the development of a lasting active immunity by means of re-tests with the Schick reaction. The toxin-antitoxin injections consisted of 1.0 c.c. of the mixture given subcutaneously in the arm at the insertion of the deltoid and repeated twice at intervals of seven days. Not only was an active immunity produced in over 95 per cent of susceptible individuals, but we have found that this active immunity has persisted for five years, that is up to the present time and it is possible that it will continue for the life time of the individuals. This, of course, indicates that we have at our disposal today the means by which the susceptible part of the population can be protected, diphtheria controlled and finally eradicated.

The mixtures of toxin-antitoxin must be prepared in reliable laboratories and carefully tested. We have established a standard, which we believe it is safe to follow. The mixture should be of such strength that 5 c.c. injected into a guinea pig will produce a local induration at the site of injection followed by late paralysis, but will never cause acute death of the animal. Each c.c. of the toxin-antitoxin preparation supplied by the Research Laboratory contains 3 L+ doses of toxin and 3.5 units of antitoxin. With a stronger toxin, which can occasionally be produced, mixtures of toxin-antitoxin can be prepared which will contain more than 3 L+ doses per c.c.: for instance, mixtures of 4, 5, or 6 L+ doses with a corresponding increase in the amount of antitoxin. Such mixtures are slightly more efficient. We considered it advisable, however, to adopt a standard strength. If desired, the dose of the mixture can be increased to 2.0 c.c., although even with the larger doses a few individuals will be found who seem to be refractory to active immunization. In such individuals we usually find that the giving of a second series of injections of toxin-antitoxin at the end of three months, when the Schick retest is made, will bring about an active immunity. Many thousands of injections have been given with the toxin-antitoxin preparation of the Research Laboratory *and not a single untoward*

result was observed. Through some unfortunate error one of the commercial laboratories sent to one of the southern cities a mixture of toxin-antitoxin which proved later to be highly toxic to the guinea pig. There were some eight or nine deaths among the injected children. Such an accident which is most deplorable is no argument, however, against the use of toxin-antitoxin. It emphasizes the fact that extreme care must be used in making and testing the mixtures of toxin-antitoxin, before they are sent out. According to our experience, however, mixtures that are safe when sent out will always remain safe with regard to their toxic strength and will be effective for immunization for at least six months.

IV. PRACTICAL APPLICATIONS OF THE SCHICK TEST

(a) The Schick test should be used in the home where a child has developed diphtheria. By testing the other children and adults the susceptible individuals are found. Each of these is then injected at once with a prophylactic dose of antitoxin in the usual way to produce an immediate passive immunity. The delay of forty-eight hours necessary for the reading of the Schick test has little danger connected with it and has the advantage of avoiding the injection of antitoxin into those who do not need it. However, in the case of young children who have been in close contact with the disease and who cannot be observed during the next forty-eight hours it will under certain conditions be safer to give prophylactic injections of antitoxin at once without waiting for the Schick test.

(b) During an outbreak of diphtheria in institutions and schools, the application of the Schick test will enable us to select the susceptible children, who may be only 20 to 25 per cent of the total, and immunize them with antitoxin. We shall thus be able rapidly to control an outbreak of diphtheria in an institution or school.

(c) The Schick test is of great value as a routine procedure in contagious disease hospitals, various other hospitals, and in many institutions and homes caring for children, such as orphan and infant asylums, day nurseries, public and private schools, etc.

(d) In private and institution practice it is important that the physician should know whether the children are susceptible or immune to diphtheria, even when there is no outbreak of the disease and there is no immediate danger. One very important fact should be emphasized. We have found that children over two years of age who give negative Schick reactions will continue to give such reactions over a period of years if the same technic and the same standard dilution of toxin is used in making the test. It seems, therefore, that such natural immunity persists for a long period of years and possibly for life. The fact that the negative Schick reaction in the naturally immune individuals indicates a long and persistent immunity adds great value to the use of the test in homes, institutions, schools, etc.

(e) In the routine prophylactic work in diphtheria, when there is no immediate danger from the disease, we should use the Schick test in conjunction with the active immunization with toxin-antitoxin. The work is so well established now that we had no hesitancy in asking the school authorities in New York City to allow us to apply the Schick test to all the children in 100 selected

schools. This work will be started on a large scale in the various schools in the different boroughs. With the consent of the parents the children giving positive reactions will be injected with toxin-antitoxin. Subsequently those receiving the immunizing injections of toxin-antitoxin will be re-tested with the Schick test to determine the development of an active immunity.

CONCLUSIONS

1. Diphtheria is a widely prevalent disease with a morbidity and mortality which have remained fairly constant during the past ten years.

2. Active immunization with toxin-antitoxin of all young children from six months to two years of age is essential in bringing up a diphtheria-immune population.

3. The Schick test and control test should be applied to all children over two years of age, and all those giving a positive reaction should be actively immunized with toxin-antitoxin.

4. The Schick test and toxin-antitoxin immunization will find great fields of usefulness in homes, in various schools, institutions, hospitals, etc.

5. Diphtheria outbreaks can be completely controlled in homes, institutions, and schools by promptly applying the Schick test and by giving prophylactic injections of antitoxin to the susceptible individuals.

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OBSERVATIONS ON THE MOTILITY OF THE ANTRUM AND THE RELATION OF RHYTHMIC ACTIVITY OF THE PYLORIC SPHINCTER TO THAT OF THE ANTRUM*

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IN a previous communication it was shown that the pyloric sphincter of the dog possessed the property of rhythmic contractility.[1] Unfinished observations at that time indicated that such motor activity of the sphincter was influenced by and coordinated with the activities of the antrum. The experiments here reported substantiate our previous statements relative to the sphincter and definitely show that the activities of the sphincter are influenced by those of the antrum.

REVIEW OF BIBLIOGRAPHY

According to a number of observers the peristaltic waves of the pars media are differentiated from the characteristic motility of the preantral and antral regions. The more commonly accepted view, however, is that the entire course of a contraction wave of the stomach is simply peristaltic in nature and that it does not differ in character from similar waves in the intestine.

In 1886 Hofmeister and Schütz[2] studied the excised and bloodless stomach of the dog in a moist chamber. In such preparations a contraction wave appears a few centimeters from the cardia, moves peristaltically to a point about 2 cm. from the antrum at which point a deep, preantral contraction occurs, after which the "sphincter antri" contracts. This is followed by relaxation of the preantral contraction and a maximal contraction of the "antral sphincter" of sufficient strength to separate the antrum from the rest of the cavity of the stomach. During the height of contraction of the "antral sphincter" the musculature of the antrum as a whole contracts, the latter usually being preceded by a strong shortening of the antrum. Prior to this observation, Morat, 1882,[3] obtained graphic records of gastric motility by means of a large rubber balloon inflated with air. By use of the manometric method von Pfüngen, 1887,[4] observed on an average three contractions of the antrum per minute, each of which lasted from 6 to 12 seconds. Von Moritz, 1895,[5] by means of an elastic balloon of moderate size attached to a sound passed through the esophagus, recorded the variations of gastric pressure and motility. According to this author the fundus and pyloric antrum show different functions; the former a digestive, the latter a motor function as shown by the appearance of rhythmical contractions at the rate of from 2 to 6 per minute. The works of Cannon, 1898,[6] and Roux and Balthazard, 1898,[7] clearly show that the pyloric portion is mechanically the most active part of the stomach. Radiographically the pyloric portion exhibits "peristaltic movements" throughout the entire

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period of digestion. Luciani[8] states that "the movements of the pyloric antrum are set up in the part nearest the fundus (preantral contractions) and are mainly affected by the circular fibers." Ducceschi, 1897,[9] working on dogs previously provided with a gastric fistula and six hours after a meal found that a small balloon inserted into the pyloric antrum recorded a distinct form of rhythmic movements. These movements were characterized by contractions and relaxations in regular succession; each cycle being completed within 10 to 30 seconds.

J. Auer's[10] excellent paper on the motility of the rabbit's stomach strongly supports the contentions of the older school. He summarizes his results as follows: "From observations made on normal rabbits by inspection and by the amplification of these data by operative exposure of the stomach after the innervation of the viscus had been modified, it was found that a gastric wave of contraction is usually composed of two well-defined phases which, at the height of digestion, succeed each other in orderly fashion. During the first phase a contraction appears on the stomach near the esophageal insertion and travels peristaltically to the sphincter antri, apparently skipping in its course an angular section of the preantrum, the constriction at the beginning of the preantrum being maintained. During the second phase the sphincter antri contracts strongly, and during this contraction the rest of the antrum contracts *in toto,* moving towards the preantrum, and expelling the antral contents largely or entirely into the preantrum, causing the latter to bulge markedly. The antrum then relaxes slowly and with this relaxation the preantrum sinks away usually without signs of peristalsis." Hence, "a complete gastric wave of contraction in the rabbit seems to be produced by the orderly interaction of two more or less independent parts, one of which originates in the middle of the stomach near the esophagus, and the other in the neighborhood of the preantral muscle sling. Either part may occur without the other."

The latter statement of Auer would lead to the assumption of a dual set of excitors to motility in the two portions of the stomach, however, the work of Alvarez[18] has shown that under normal conditions the stomach follows gradients of irritability, rhythmicity and latent period from the cardia to pylorus.

Cole,[11] from a study of serial radiographs of the human stomach, has shown that the sphincter bears a definite relationship to the antrum. That is, the amount of contraction of the sphincter is in proportion to the activities of gastric waves. When the gastric peristalsis is feeble the contractions of the sphincter are weak; when the gastric movements are strong, the sphincter is more strongly contracted. He has further shown that during the "systole" or active phase of every gastric cycle the pyloric ring is open and a small amount of gastric contents is propelled through its lumen into the "reservoir cap." The "terminal peristaltic wave" which has meanwhile been advancing toward the pyloric ring, upon reaching the sphincter, effects its closure so that the lumen is entirely obliterated, or visible only as a thin line.

The paper by Luckhardt, Phillips and Carlson[12] is of special interest at this point. They observed both graphically and fluoroscopically that in man the "pylorus" opens for the ejection of chyme with the arrival at the pyloric sphincter of powerful advancing rings of contraction aided possibly by a general

increase in tone of the musculature of the stomach as a whole. In dogs the gastric content was observed to issue from a duodenostomy either during a marked rise in gastric activity, or more commonly just at or after the peristaltic wave passing over the stomach had affected its greatest increase in intragastric pressure. They further demonstrated that a more definite relation exists between the muscular activity of the stomach and the opening of the pyloric sphincter than between the opening of the sphincter and the reaction of the gastric contents. In discussing their observations in relation to the findings of Alvarez, they state: "With a gradient higher in the body of the stomach than near the pylorus, the increased pressure coming from above effects the opening of the pylorus even before the free acidity has reached a concentration sufficient to assure chemical control of the sphincter." Their graphs are most instructive and convincing. Just prior to the above report Ivy[13] made the observation that water issued from the dog's stomach in such a manner as to indicate a dependence upon the peristaltic waves in the stomach.*

Such observations definitely establish the antrum as an organ of special motility, the purpose of which is to mix the ingesta and bring it into contact with the gastric juices, and to propel the semidigested chyme onward into the duodenum. Save for the observations of Cole and Luckhardt, Phillips and Carlson, but little definite work has been done on the relation of motility in the antrum to that of the sphincter. The lack of information concerning the motor relation between the antrum and sphincter is, no doubt, the result of the usually accepted theory of an "acid control of the pylorus." Cole drew his conclusions from a study of serial radiographs of the human stomach. Luckhardt, Phillips and Carlson observed the egress of gastric contents from a duodenal fistula in relation to pressure changes in the stomach. Their results were also checked radiographically, both in the dog and man. Many observers have used the balloon method to study motility in the filled or empty stomach. However, we have failed to find any record of simultaneous tracings obtained from the antrum and sphincter. The motor relations between the sphincter and antrum, here reported, are the results of studies of simultaneous tracings obtained from these two parts.

FUNCTIONAL ANATOMY OF THE PARS PYLORICA

A brief description of the structure of the terminal portion of the stomach seems to be justifiable in order to make clear the results obtained by graphic procedures.

The pars pylorica of the dog's stomach is structurally the equivalent of a vent the diameter of which diminishes progressively toward the pyloric sphincter. (Fig. 1.) The inner wall of the right portion of the stomach shows the orifice which constitutes the entrance to the pars pylorica clearly defined. The upper rim of the orifice which is coincident with the incisura angularis forms a definite ring which in its course becomes attenuated to aid in the formation of the wall of the vestibule on the greater curvature. The angle of descent of the

*Since the completion of this paper McClure, Reynolds and Schwartz,[16] from fluoroscopic studies, assert that under normal conditions the human pyloric sphincter opens regularly at the approach of each antral peristaltic wave, allows chyme to pass through into the duodenum during an appreciable length of time, and closes when the antral peristaltic wave has spent itself. They further report that acid is not the principal factor controlling the opening and closing of the pyloric sphincter in men.

fibers in this structure decreases to a point opposite the incisura angularis. By reason of this distribution of the circular fibers the vestibule or preantral region assumes the form of a triangle the apex of which is at the rim of muscle forming the incisura. This condition is graphically shown in Fig. 1, in which the triangle is indicated as formed by that portion of the stomach lying within points I A, X and C. The pars pylorica, or outlet of the stomach, therefore, may be considered as arising at the incisura angularis on the lesser curvature and a point opposite on the greater curvature where the circular fibers lie in a plane transverse to the long axis of the antrum. The terminal portion of this region is represented by an accumulation of circular fibers which form the pyloric sphincter, or valvula pylori, B.N.A. In the majority of the dogs observed the

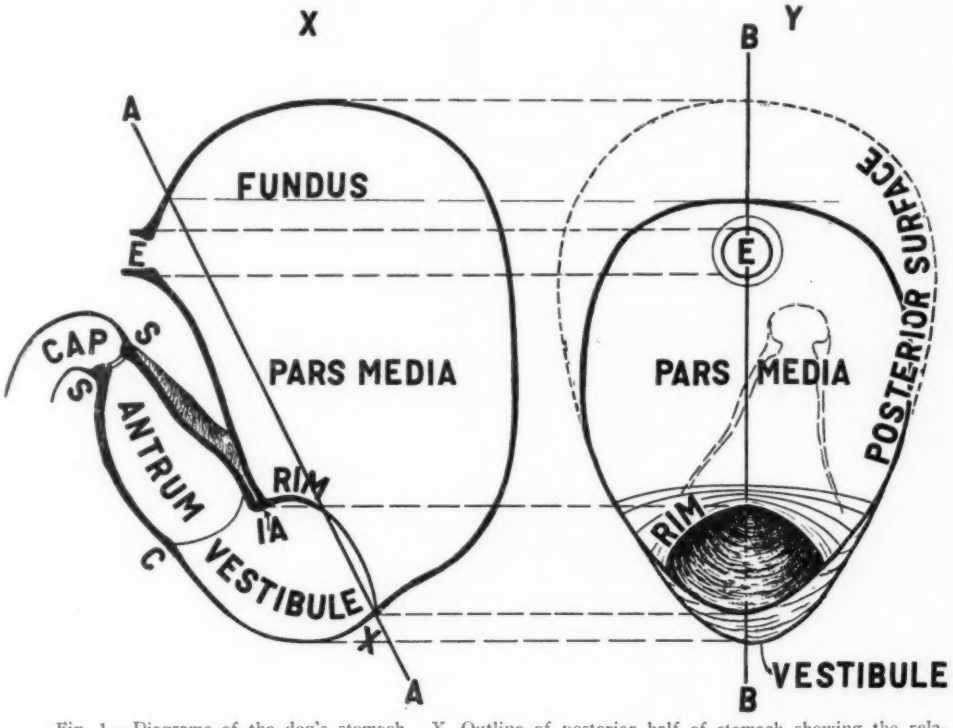

Fig. 1.—Diagrams of the dog's stomach. *X*. Outline of posterior half of stomach showing the relation of the fundus to the vestibule, antrum and sphincter, *S*. *Cap*. Duodenal cap or beginning of the small intestine. *AA*. Line of incision of stomach to show the right half of the stomach. Note the formation of the outlet and the relation of the vestibule to the antrum.

musculature of the sphincter was accentuated on the greater curvature. The pyloric canal is a rather variable factor, although it is usually described as the aperture leading from the terminal portion of the antrum into the duodenum. Functionally the extent of the canal is determined by the amount of muscle involved in an antral contraction plus sphincteric action for, as will be shown later, the pyloric ring only represents an accumulation of functional units of the terminal portion of the antrum.

EXPERIMENTAL METHODS

The observations here reported were made upon 44 operated and normal dogs. All operative procedures were carried out under ether anesthesia.

Graphic records were obtained both on the anesthetized and conscious animals following the operation at various intervals. Briefly, the operation consisted of passing an enterograph into the pyloric canal and antrum through an incision in the fundic portion of the stomach. After securing the recording apparatus in position the opening in the stomach was closed by a purse-string suture about one or more tubes leading from the placed apparatus. Aseptic precautions were observed in all cases in which the animal was permitted to live for a period longer than 12 hours.

The various types of apparatus used for obtaining graphic results of antral

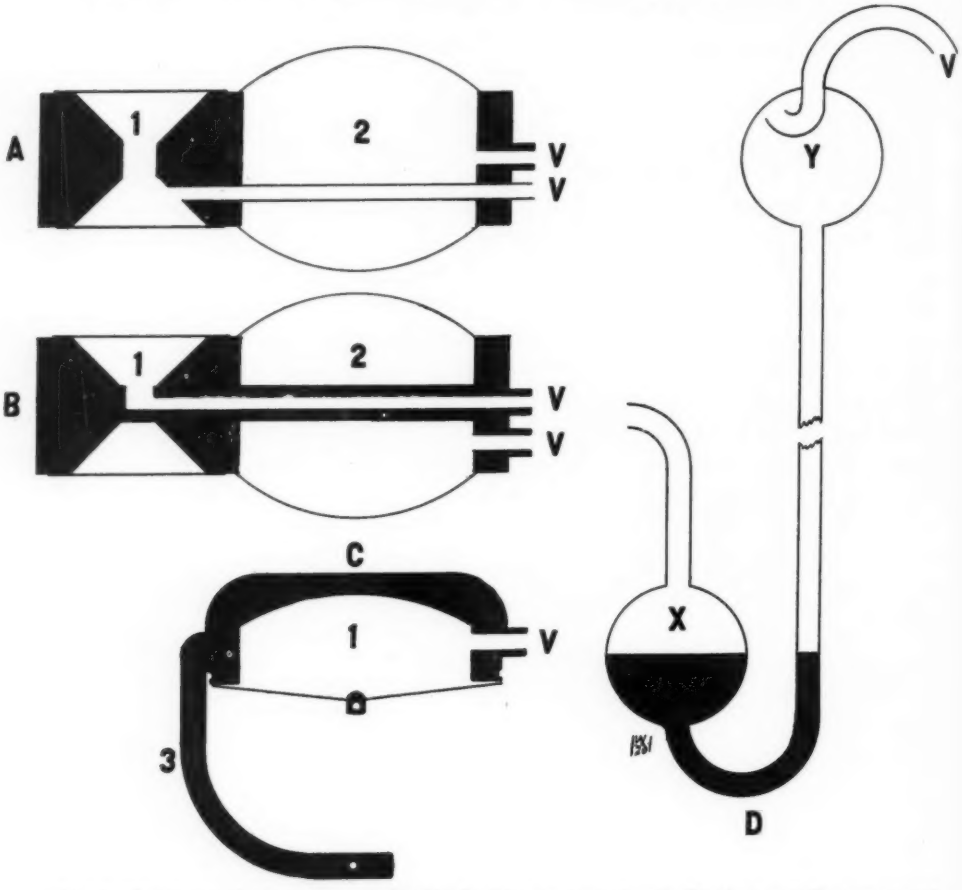

Fig. 2.—Diagrams of apparatus. *A*. Double flexible enterograph. *B*. Rigid or spindle enterograph. *1*. Air chamber in pyloric canal; *2*. in antrum. *V*. Vents leading to water manometers; *C*. tambour myograph showing air chamber (*1*) and vent (*V*); *3*, rigid arm for anchorage of sphincter or segment of gut. Condom rubber used for chambers *2* of *A* and *B*; finger cot for chambers *1* of *A* and *B*. *D*. Water manometer; *X*, reservoir bowl containing water; *Y*, check bowl for receiving water should pressure force column to such a height; *V*, vent leads from chamber *Y* in such a manner as to prevent easy exit of water from bowl. This manometer was found to be of special use in obtaining traces from the human stomach.

and sphincter action are modifications of the pylorograph described in our previous paper.[1] For the sake of convenience we have termed these modified balloons enterographs. In brief they consist of two chambers, one of which occupies the pyloric canal; the other the antrum. The details of construction are shown in Fig. 2. The balloon chambers are connected by means of heavy rubber tubing with water manometers (Fig. 2-D) carrying from 5 to 20 cm.

of water pressure for balloon distention. Piston, bellows, and tambour recorders were used for registration of motility. Save for the water manometers air transmission was used entirely.

EXPERIMENTAL RESULTS

(*A.*) *Direct Observations on the Exposed Stomach.*—In the filled stomach exposed in a warm saline bath, waves of peristaltic contraction arise in the region of the pars media on the greater curvature. The constriction band then travels toward the antral region gaining in strength as it progresses. The depth of contraction is often greatest just in front of the vestibule at which point the contraction is often completed. However, the phenomena, which usually follows the arrival of a constriction band at the vestibule is a slight wave of contraction, barely visible to the naked eye, which sweeps over the entire vestibule or "preantral sling" to begin again as a powerful, progressive peristaltic wave which passes along the first part of the antrum. At times a peristaltic wave passes progressively from its origin over the vestibule and first portion of the antrum. We have seen a condition analogous to that described by Auer[10] in the rabbit in which a peristaltic wave reaches the preantral region either to cease or, after a pause, to manifest itself again in the first portion of the antrum. We have also noted antral action independent of fundic action. However, we are of the opinion that the continuous wave represents more nearly the normal movement of the moderately filled dog's stomach.

The appearance of a peristaltic wave in the region of the antrum is followed by antral activity. This motility of the antrum which begins at the right of the incisura angularis continues as a progressive movement which finally terminates in the closure of the sphincter. Therefore, a wave of motility in the dog's stomach may progress from its origin over the entire gastric surface to terminate in the closure of the sphincter. The longer diameter of the antrum was observed to contract just preceding the beginning of contraction of the circular fibers, but a simultaneous contraction of the antrum *in toto* was not observed by us. However, we have seen the entire antrum in a state of contraction sufficient to cause marked anemia of the parts. This anemia begins in the gastric end of the antrum and gradually increases in extent until the entire antrum is bloodless. At such a time the sphincter begins to lose color and this loss of color persists during the return of blood to the gastric portion of the antrum or at a time of antral relaxation. This distribution of blood in the pars pylorica is analogous to the tracings to be described later, i.e., antral contraction followed by sphincter contraction. Inhibition was observed in the antrum as a whole just before the beginning of its active phase, but was never observed to occur in antral fibers caudal to the point of constriction. On the other hand, marked relaxation follows behind the contracting portions. So marked is this wave that it might well be called an advancing wave of relaxation, which progressing over the antrum and sphincter return these structures to their quiescent phase.

(*B.*) *Graphic Observations.*—I. Rhythmic Motility of the Antrum.—The antrum, like the pyloric sphincter, demonstrates rhythmic activity. The in-

dividual cycles consist of phases of contraction, relaxation, quiescence and inhibition. These phases follow each other in an orderly sequence and are maintained for hours both in the filled and recently emptied stomach. These cycles appear at the rate of from 3 to 5 per minute, that is, each cycle re-

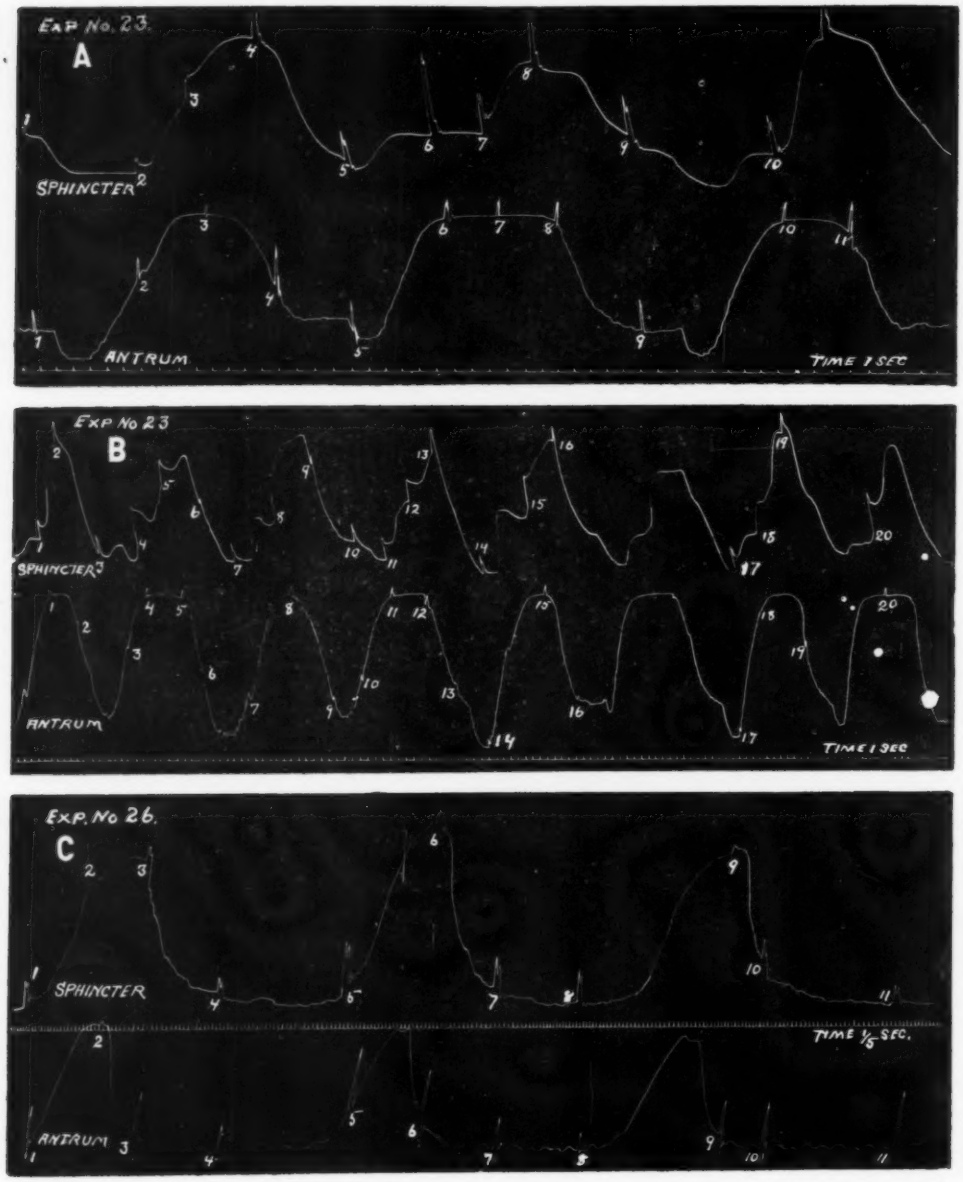

Fig. 3.—Three sets of tracings showing the relation between the antrum and sphincter. *A* and *B*. Experiment *23*; February 7, 1920. Ether used throughout the experiment. Records obtained with Marey tambour begun immediately following operation. *C*. Experiment *26*; February 14, 1920. Ether for operation; records obtained from conscious animal. Numerals indicate synchronous points.

quires from 12 to 20 seconds for its completion. Rhythmic contractions of the antrum are not lost because of a light ether anesthesia, or following denervation of the entire stomach.

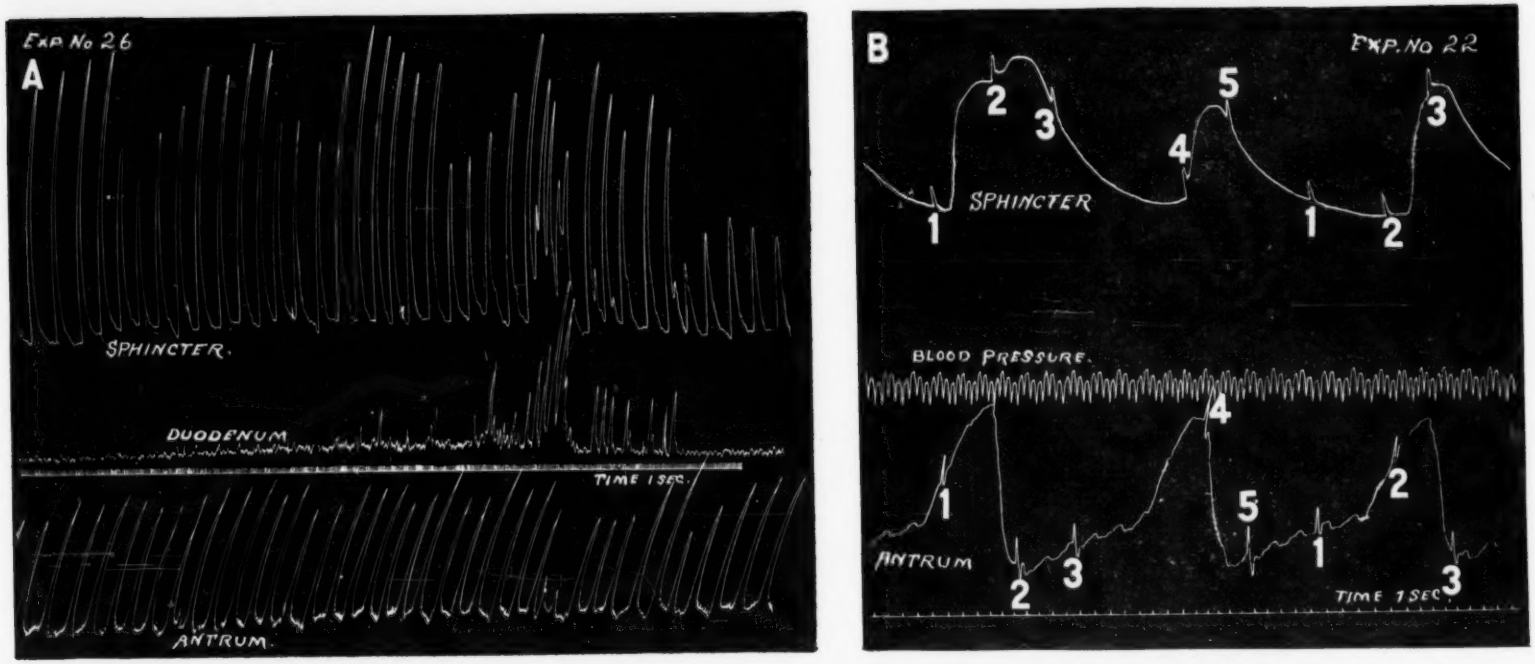

Fig. 4.—Tracings showing relation of antral to sphincteric motility. *A*. Experiment 26; February 14, 1920. Conscious animal. Trace obtained with a triple enterograph. Note alterations in antral and sphincter curves during duodenal activity. *B*. Experiment 22; February 1, 1920. Ether used during taking of records. Large antral balloon. Note relation of antral to sphincter cycles.

Characteristic antral cycles are shown graphically in Figures 3 and 4. The antral cycles shown in these two figures while analogous in character, demonstrate certain variations. The trace in Fig. 4, *B*, was obtained by using a flexible enterograph with a rather large balloon in the antrum. Such a balloon of necessity occupies the entire antrum and possibly a portion of the preantral region, hence it will transmit pressure changes occurring in the region occupied from the very beginning and throughout the contractile period of the entire antrum. With such an apparatus the greatest degree of depression in these cycles occurs as the final phase of relaxation. From this point on, tone is gained, superimposed upon which appears the phase of contraction. The wave of contraction is rapidly completed and does not demonstrate a holding phase, possibly, because of reduced pressure (inhibition or relaxation) in the preantrum and beginning portion of the antrum. Such graphs are very similar to those obtained with a free balloon in the partially filled or empty stomach. The antral tracings of Fig. 3 are typical of those obtained with a spindle enterograph, a small balloon, firmly held in position, constituting the antral portion. Such graphs demonstrate a plateau or sustained contraction following the initial rise of the lever. The plateau gradually declines at the end of the contraction phase and then the lever falls rapidly to reach its lowest point or a quiescent phase which is soon followed by a definite wave of inhibition. This latter type of response, which is well shown in Fig. 3, *A*, was the one most commonly observed in our series of experiments. In those cases where the greatest degree of relaxation follows immediately upon the contraction phase there appears a gradual upward climb of the lever, however, this is usually broken by a wave of inhibition which occurs just prior to the appearance of the positive phase.

II. Motility of the Pars Pylorica.—Direct observations of the pars pylorica at a time of active motility are difficult to interpret. However, a double enterograph, one chamber of which is inserted into the pyloric canal, the other into the antrum, gives definite information as to the functional relation of the antrum to the sphincter. Recording levers attached to the chambers of the enterograph demonstrate rhythmic activity. The movements in the two portions, however, do not occur synchronously, but they do occur rhythmically and at definite intervals of time, depending upon the distance between the two receiving chambers of the enterograph. The two levers do not necessarily bear any definite relation to each other in their degree of oscillation, although they are placed so as to give the same degree of magnification and are working under the same pressure. However, the movements of the antral lever are always more regular and less variable than those of the sphincter. At no time did a contraction of the antrum occur which was not followed by some motor responses of the sphincter (Fig. 4, *A*). Such a response might have been anticipated in view of the fact that the circular fibers constituting the sphincter represent a piling up at a definite point of the circular coat of the antrum itself.

Incidentally it may be stated that we frequently had occasion to observe the influence of abdominal and gastric incisions upon the gastric motility. It was found that while such manipulations modified gastric motility as to degree

they did not abolish it and, in fact, appeared not to interfere seriously with the emptying of the stomach. It will be noted that these findings do not agree with observations on other laboratory animals, e. g., those of Auer[17] on the rabbit. So far as we could determine by the methods employed the degree of motility of the antrum and sphincter was not perceptibly affected by ether anesthesia of a moderate depth. With the development of a deep, surgical anesthesia there resulted a gradual reduction of motility. Complete loss of motility and residual tonas could be obtained only under excessive doses of the anesthetic.[1] Graphic results obtained while the animal was under a light anesthetic and at various times following recovery from the anesthetic were of the same type and nature. However, our best results were obtained from dogs sufficiently etherized to barely abolish voluntary reflexes.

The time relations of the activities in the antrum and sphincter are shown graphically in the tracings of Figures 3 and 4. In these tracings it will be noted that the antrum, like the sphincter,[1] demonstrates cycles of rhythmic motility. The antral cycles show the same duration as those of the sphincter, however, the duration of the phases is not the same in the two structures.

The tracing of Fig. 4, *B* was obtained with a double enterograph, a large balloon constituting the antral chamber. In this tracing the antral contraction has maximally relaxed at the moment of complete contraction of the sphincter, numerals *2, 5* and *3*. The sphincter goes into action only after the antral contraction is well started, numerals, *1, 4* and *2*. The maximal relaxation of the sphincter in this trace occurs during the active phase of the antrum, on the contrary the antrum shows its greatest degree of relaxation at a time when the sphincter is actively contracting. Immediately following complete relaxation the antrum gains tone up to the point of a second positive phase. During this time the sphincter is rapidly relaxing. Hence, the trace demonstrates a constant type of alteration in the phases of the two parts. Such graphs have been taken for hours, both on the anesthetized and conscious dogs without showing alterations in the response between the antrum and sphincter. The three tracings shown in Fig. 3 were obtained with a rigid, double enterograph, a small balloon constituting the antral chamber (Fig. 2, *B*). Inhibition in the antrum preceding a contraction is well shown in the trace *A*, and in the last 4 cycles of trace *B*. In trace *C* no definite phase of inhibition is shown preceding the phase of contraction. A similar condition holds for the sphincter. In this trace a decided phase of quiescence is common to both antrum and sphincter, although the active phases in the two parts are the same as those described above. In traces *A* and *B* the sphincter demonstrates a more or less well defined relaxation or inhibition which occurs during the active phase of the antrum. In the graphs of Fig. 3 and Fig. 4, *B*, the sphincter demonstrates its active phase in such a manner as to reach its maximum while the antrum is relaxing, also the sphincter shows its greatest degree of relaxation during the first portion of the active phase of the antrum.

The irregularities in the sphincter curves as shown at points *6* to *7*, and *10*, of Fig. 3, *A*, and those of trace *B*, of the same plate appear to result because of activities of the duodenum. During the registration of trace *C* the duodenum was observed to be in a quiescent state, and it will be noted that the rise and

fall of the sphincter curve is uniform. Later in the experiment, however, the duodenum did demonstrate rhythmic or segmental action for a short period, and during this period alterations occurred in the activities of the sphincter, Fig. 4, *A*. In spite of the variations in sphincteric action the relation of its major activities to that of the antrum is maintained. The relation of duodenal activity to that of the antrum and sphincter is now under consideration and will be reported in a later paper.

Results of a similar nature were obtained by the use of a tambour myograph (Fig. 2, *C*) applied to the exterior of the sphincter and a balloon of moderate size in the antrum (Fig. 5). In this case, as elsewhere, the antral contraction is followed by a sphincteric contraction which reaches its height during the period of relaxation of the antrum.

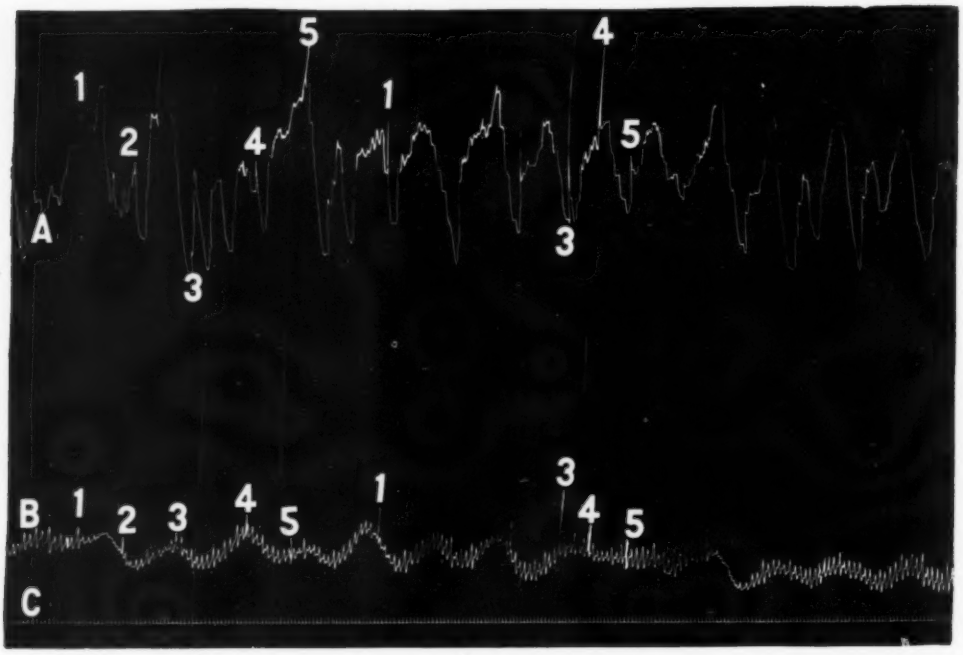

Fig. 5.—Experiment 27; February 19, 1920. Ether used throughout. Animal immersed in tank of warm saline. *A*. Sphincter contractions obtained with tambour myograph (Fig. 2*c*). Because of the structure of the myograph the down stroke in the trace represents contraction. *B*. Gastric motility obtained by using a small free balloon in the stomach.

The results of our graphic observations are similar in nature to those obtained by direct observation of the stomach, namely, blanching of the antrum during its positive phase followed by loss of color in the sphincter when it enters upon its contraction phase. This loss of color in the sphincter occurs at a time of rapid return of color in the antrum; the flush in the sphincter appearing again with the blanching of the first part of the antrum.

Such results definitely show that the antrum enters upon and reaches its height of contraction at a time when the sphincter is relaxing or quiescent and that the sphincter goes into action some time later to reach the height of its contraction at a time when the antrum is beginning to relax or is rapidly relaxing. A period of quiescence, or relaxation, is then common to both antrum

and sphincter. The sphincter and antrum both invariably show some degree of relaxation (inhibition) immediately prior to their active phases; the sphincter demonstrating inhibition during the active phase of the antrum, and the antrum during the period of relaxation of the sphincter. Hence, the activities of the antrum and sphincter taken together may be considered as constituting a *cycle of the pars pylorica.*

The duration of the phases, as indicated above, is not the same in the two portions of the pars pylorica, neither do they develop their maximal activity simultaneously. The sphincter contraction begins at a time when the antral contraction is already practically maximal and does not reach its maximum until the antral contraction has disappeared. That is, the phase of contraction of the sphincter covers the period of sustained contraction and the greater portion of the relaxation phase of the antrum. The sphincter, therefore, acts in such a manner as to cover a negative phase in the antrum and add, on the average, 2 and ½ seconds to the positive phase of the pars pylorica. Thus it will be seen that the sphincter's contraction serves to supplement that of the antrum and to guard against the return of material that has been forced into the duodenum by the preceding antral contraction. Inhibition of a more or less marked degree immediately precedes the development of the positive phase of the cycle in both the antrum and sphincter. In the sphincter the occurrence of this inhibition is usually simultaneous with the development of the active or contraction phase of the antrum. This inhibition of the sphincter may be regarded, therefore, as an example of Langley's law of the intestine since it removes the tonus of the normal antagonist of the antrum and facilitates thereby the antral function.

If the above conclusions are justifiable then the activities of the two parts (antrum and sphincter) must be coordinated and to a high degree dependent upon each other. In other words, the activity of the lower segment should depend upon the reception of waves of excitation and inhibition passed into it from the segment above. The results reported appear to justify such conclusions, however, the following experiments were performed to determine whether or not such a condition subtends for this region of the stomach.

Immediately following the operation for the placement of a pylorograph (surgical anesthesia) and while the stomach was in a state of inactivity the effects of electrical stimulation of the antrum upon the sphincter were noted. Graphic results of such procedures are shown in Fig. 6. Curve *3* in this figure represents the motor response of the sphincter to an electrical stimulus applied to the stomach 2 and ½ inches from the sphincter. This curve, obtained by the use of the pylorograph, demonstrates a characteristic wave of contraction and relaxation after a latent period of 4 and ½ seconds. A similar curve is shown at *4* in the same figure. The small secondary responses in these two tracings were observed to occur in conjunction with a wave of motility in the first part of the duodenum. Direct stimulation over the sphincter also caused it to contract, usually after a latent period of but 1 to 2 seconds, curve *5*. Similar results were obtained following stimulation of the first part of the duodenum, curves *6* and *7*. Results of the same nature may be obtained on the active stomach.

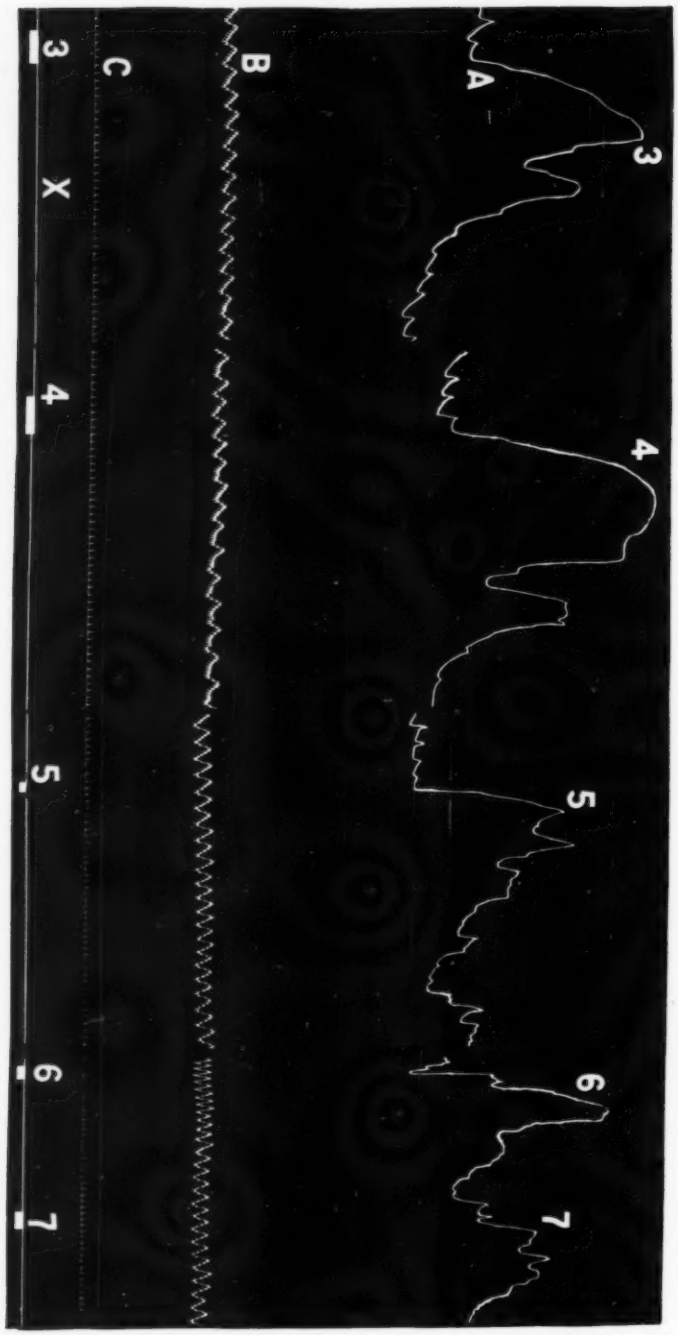

Fig. 6.—Tracings showing the results of electrical stimulation of various parts of the quiet stomach and duodenum on the sphincter. *3*. Sphincter contraction following stimulation of the stomach 2½ inches from the pyloric ring. *4*. Stimulation of the antrum 1 inch from sphincter. *5*. Stimulation above sphincter. *6* and *7*. Stimulation of the duodenum. All curves were obtained from a nonrhythmic stomach. *B*. Blood pressure. *C*. Time in seconds.

This experiment, which is typical of the series of similar observations, seems to point to a motor control of the sphincter because of impulses transmitted to it through the antrum. However, this experiment does not directly show inhibition of the sphincter as the result of antral activity. This may be accounted for upon the assumption that a quiet and more or less atonic preparation fails to register other than contractile phenomena. Therefore, inasmuch as a definite latent period exists between the application of a stimulus to the antrum and a positive phase in the sphincter, the length of the latent period depending upon the distance of the electrode from the sphincter, it may be assumed that the sphincter is not excited because of the stimulation applied to the antrum but by the transmission of a positive wave of contraction which passes over the pars pylorica.

III. Radiographic and Graphic Results.—The above reported results, if correct, should be observable in the unoperated animal by means of the x-rays. That is, if the antrum and sphincter demonstrate coordinated motility, radiograms taken at short intervals during the passage of an opaque meal from the stomach should show a constant relation in the distribution of the meal during the same phase of activity in any given part of the stomach. That this is so for man has been clearly shown by the studies of Cole. Luckhardt, Phillips and Carlson who observed fluoroscopically the exit of an opaque meal in dogs provided with a duodenal fistula, also found that the activities of the sphincter bore a definite relation to those of the antrum.

The three drawings in Fig. 7, *A* represent the form relation of the antrum to the sphincter during a characteristic cycle of the pars pylorica. In No. *3* the antrum is shown pouring its contents through the widely relaxed sphincter into the duodenum, the size of the antrum is much reduced, and the sphincteric canal and duodenum are engorged with the barium mixture. Following this stage the sphincter actively closes as is shown in No. 4, by the narrow hairline of barium connecting the duodenum and antrum. At this time the antrum shows rapid relaxation as indicated by the increase in size and loss of tonicity. Relaxation of the antrum continues from this point on as is shown by the changes in the position of barium in this region and the stomach as a whole. In the last cut the stomach as a whole demonstrates an inactive phase although the duodenum shows active segmentation. The sphincter during this time of complete antral relaxation (diastole) is free of barium, as shown in No. 5. These three drawings from a series of successive radiograms obtained from a normal dog's stomach are equivalent in nature to the results obtained by direct observation and by the use of graphic means; that is, the antrum is actively contracting to pass material into the duodenum at a time of quiescence on the part of the sphincter, and the sphincter is closed during the period of beginning relaxation of the antrum; an inactive period associated with different tone levels then being common to both.

The relation of the sphincter to the antrum was further studied by combining radiographic and graphic methods. This was accomplished graphically by securing an open pylorograph—the equivalent of an open cylindrical balloon—in the pyloric canal.[1] This device permits the recording of the sphincter's motility and at the same time allows the stomach to pass its contents into the

small intestine. The animal was permitted to recover from the operation, (usually twenty-four hours), at which time graphic records were begun. Following this a barium mixture was given by means of the stomach tube. With the graphic method it was possible to take radiograms at will, of any phase of the sphincter's action. Such radiograms not only show the position of the sphincter but also the position of the barium in all parts of the stomach and

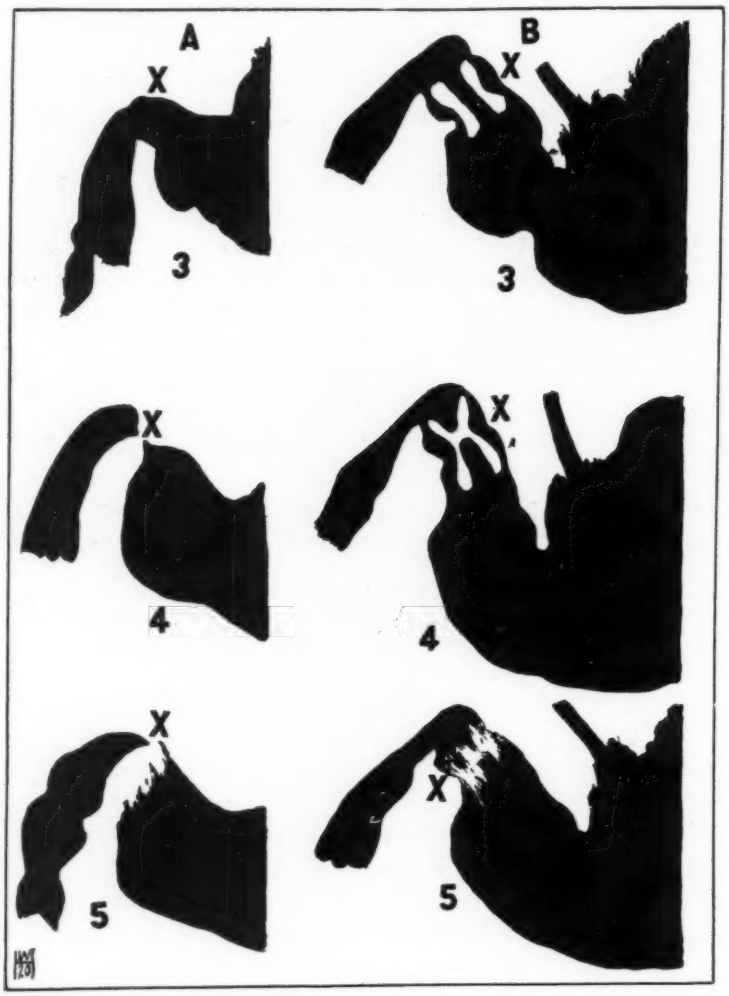

Fig. 7.—Drawings from radiograms showing the relation of the antrum to the sphincter. *A*. Experiment 32; February 18, 1920. Normal dog starved 5 hours. *B*. Experiment 24. Barium mixture by tube 24 hours after placing open pylorograph in the pyloric canal. Animal conscious. Light areas indicate air chamber of enterograph. In *B*, *3*, barium is passing through tunnel of enterograph. In *4* the inner walls of the tunnel are shown cutting off the passage of barium from the stomach. In *5* the apparatus outline is indefinite; barium in antrum under low tension. *X*, Sphincter.

duodenum. Hence, with this method it was possible to obtain graphic tracings which were characteristic for the sphincter, and also radiograms which were identical in principle to those shown in Fig. 7 from the normal stomach.

The tracings in Fig. 8 are graphic records of the sphincter's action as obtained with the open pylorograph. The numerals *3*, *4* and *5* indicate points

at which radiograms were taken. The radiograms are reproduced in Fig. 7, *B*, Nos. *3*, *4* and *5*. Radiogram 3 was taken just before the lever of the recording apparatus began to ascend, or at a time of active contraction of the antrum. Picture *4* was taken just as the pyloric sphincter reached its highest point of contraction, Fig. 8, No. *4*, and at a time of beginning relaxation of the antrum (Fig. 7, No. 4). It will be noted that the ring of contraction in No. *3* of Fig. 7, *B* is not present in No. *4*, also that the line of barium passing through the tunnel of the pylorograph is discontinued in No. *4*. This condition, therefore, is the equivalent of that shown in Fig. 7, *A*, No. *4* which was obtained from a normal stomach. Picture *5* of Fig. 7, *B*, was obtained immediately following relaxation of the sphincter as shown by the recording lever, Fig. 8, No. *5*. This

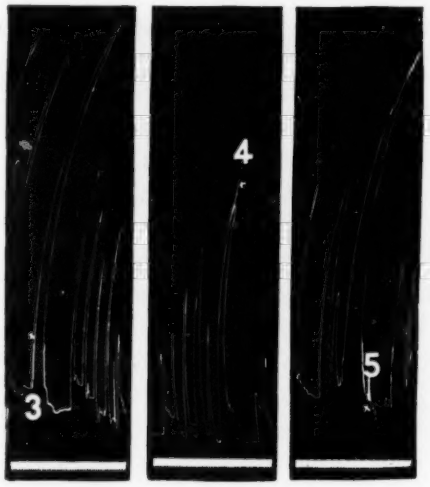

Fig. 8.—Experiment 24; February 9, 1920. Tracings obtained by use of open pylorograph. Radiograms in Fig. 7, *B* 3 4 5, were taken at points marked *3*, *4*, *5*. Time 2½ seconds.

cut which is the equivalent of No. *5* in Fig. 7, *B* shows the antrum and stomach as a whole to be in a state of relaxation or quiescence preparatory to a second antral cycle. Barium is not present in the tunnel of the pylorograph, hence, antral pressure is not sufficiently strong to force material forward during its quiescent phase. The same condition due to sphincter tone is shown in No. *5* of Fig. 7, *A*.

These results seem to us of special importance for they clearly show that the activities of the stomach are not materially altered because of the presence of a foreign body in the pyloric canal through which the gastric contents may pass. Also the results of this procedure are equivalent to those obtained by other procedures. Therefore, the relationship between the activities of the sphincter and antrum above described may be taken as indicative of the normal relation existing between these two parts of the stomach.

DISCUSSION

Sources in error in the interpretation of results due to operative procedures have been eliminated only to the extent to which the results obtained by means of the x-rays may be relied upon. According to our results there is apparently no

qualitative difference in the movements of normal and operated stomachs if sufficient time is allowed for the latter to resume activity following operation. Our observations are in accord with the prevalent idea that the intestines may remain motionless for some time following laparotomy. On the other hand, movements begin in the stomach of the dog shortly after the abdomen is closed. The presence of a foreign body in the antrum and pyloric canal may influence motility. The results here reported seem to indicate that the antrum reacts in the same manner in the presence of a balloon as it does in the presence of food. We feel that the presence of the apparatus does not alter the nature of gastric motility.

The results obtained from observations on the excised stomach or from graphic records obtained by means of balloons or surgical procedures, it is true, are difficult to interpret and are open to severe criticism. The inability of a free elastic balloon in the stomach to properly transmit gastric motor changes has recently been emphasized by Luckhardt, Phillips and Carlson.[12] In conformity with their statements, we were unable to show by such a method any degree of uniformity between graphic records and radiographic findings. This is especially true when the stomach is partially filled, because at such a time the balloon will rise to the surface of the gastric content. This was observed on experimental animals and also in human subjects. However, a small balloon or enterograph secured in the antrum and carrying a pressure equal to from 5 to 15 cm. of water will transmit rhythmic oscillations to a recording apparatus, the results of which are analogous to those observed directly and radiographically. Such oscillations, as described by Ducceschi, 1897, appear rhythmically and consist of cycles composed of a contraction, a relaxation, a quiescent and an inhibition phase. Such contractions, like those of the sphincter, are maintained for hours in both the conscious and anesthetized animal whether the stomach contains food or has been recently emptied.

Since the work of Cannon[19] the opening and closing of the "pylorus" has been ascribed to an acid control. However, Ducceschi[9] had previously shown that the introduction of a 0.15 per cent hydrochloric acid solution into the vicinity of the cardia and fundus excites typical peristaltic waves. In the region of the antrum a 0.10 per cent solution produced a delay in the rhythm while stronger solutions weakened the intensity of antral contractions and altered their course. The theory of an acid control of the pylorus has never explained certain phenomena associated with the emptying of the stomach. The same is true of the theory of fluidity. Certain clinical and experimental observations have definitely shown that factors other than acid are directly concerned in the phenomena of gastric evacuation. Neilson and Lipsitz,[14] for instance, have shown that posture to a great extent determines the time of retention of water in the stomach. Furthermore, Spencer, Meyer, Rehfuss and Hawk[15] have shown that a 1 per cent solution of sodium bicarbonate hastens the emptying of the stomach either by increasing its motility or by opening of the "pylorus." They have further shown that hydrochloric acid is not necessary for the opening of the stomach for it empties, at times, when its contents are alkaline.

The radiographic studies of Cole,[11] while apparently not undertaken to disprove the theory of an "acid control of the pylorus," has done much to arouse suspicion concerning it. According to this observer the amount of contraction of the pylorus is in proportion to the activity of the gastric peristalsis, that is, when the gastric peristalsis is feeble the contraction of the sphincter is weak, and when the gastric peristalsis is strong the sphincter is more tightly contracted. In the earlier stages, when the gastric peristalsis is active, the muscle of the sphincter contracts tightly, as peristalsis grows more feeble the contractions of the sphincter become less intense until during the later stages of digestion, it is greatly relaxed as shown by the comparatively large lumen. During the systole of every gastric cycle, according to Cole the pylorus is open and through its lumen a small amount of liquid chyme is propelled into the reservoir cap. The terminal peristaltic contraction which has meanwhile been advancing over the antrum, upon attaining the sphincter effects its closure, so that the lumen is entirely obliterated or visible as a small line. Our radiograms upon the dog, see Fig. 7, are similar to those published by Cole. However, our graphic results show that the sphincter enters upon its positive phase sometime after the antrum has begun to contract and reaches its height only after the antrum is well along on its phase of relaxation. Further, our tracings show that not only the positive phase of the sphincter is influenced because of the propagation of a contraction wave into it from the antrum but also by the wave of relaxation which follows the contracting wave. This wave of necessity appears at the sphincter after having traveled the length of the antrum, that is, the sphincter demonstrates a phase of relaxation which is the continuation of the relaxation wave of the antrum. Hence, in a moderately active stomach a phase of inactivity is common to the antrum and sphincter; the sphincter remaining open or relaxed save for the degree of residual tone until such a time as its fibers are excited to contraction because of the approach of a contraction wave through the antrum.

The tracings shown in the work of Luckhardt, Phillips and Carlson,[12] are corroborative of this last statement. These tracings clearly show that during an increase in tone of the stomach or at the approach of a powerful advancing ring of contraction material is forced from the stomach in ever increasing amounts, the final rush of material occurring with the termination of the peristaltic wave, and just prior to closure of the sphincter.

The motility in the antrum may be termed a compression wave which, from its origin at the proximal end of the antrum, by a process of constriction gradually presses down upon its contents. This constriction involves progressively rings of circular muscle nearer and nearer the sphincter and passes over the antrum at such a rate that the circular muscle next to the sphincter goes into a state of strong contraction before those at the proximal end have begun to relax. In other words, the advancing edge of the cycle in the antrum proceeds from above downward in the form of a wave but the duration of the constriction in the individual ring of circular muscle is so long that the entire antrum is in a state of contraction at the same time. Relaxation in the antrum follows the same order, namely, it appears first in the proximal end and gradually progresses

toward the sphincter. This perhaps means that the time of contraction stated in terms of the individual muscle fiber is uniform throughout the antrum.

In relation to the pars pylorica this compression wave in its progress involves more and more of the functional units, until those of the sphincter are reached and brought into action. The wave is also characterized by the holding quality of fibers already in action while new units are entering upon their active phase. For this reason the entire antrum may be seen to hold itself in a state of complete contraction at a time when the sphincter is just beginning to enter upon its positive phase. Relaxation always begins in the portion which first went into action and passes progressively over the pars pylorica. Therefore, the sphincter is the last portion of the pars pylorica to go into action and also the last to relax during a cycle of this portion of the stomach.

The above considerations lead to the assumption that the sphincter is opened during its quiescent phase (inhibition), either because of the pressure exerted upon it, by reason of an increased pressure in the antrum, which is associated with an increased degree of tonicity of the stomach as a whole, or because of a wave of inhibition continued from the antrum. This latter seems the more justifiable for the reason that the positive and negative phases of the antrum and sphincter are so placed that they cause the material in the stomach to be thrown forward. Also the manner of passage of the material through the sphincter is associated with the positive phase of the antrum and ceases when the sphincter contracts. Therefore, in regard to the stomach the sphincter demonstrates the "law of the intestine," i.e., it opens or is inhibited during the passage of materials and closes (contracts) when the advancing ring of contraction reaches it through the antrum.

SUMMARY AND CONCLUSION

To recapitulate, our results may be summarized as follows: Direct, graphic and radiographic observations show that the antrum and pyloric sphincters are rhythmical in action, that is, contractions and relaxations follow each other in a regular sequence. These rhythmical actions or cycles occur at the rate of from 3 to 5 per minute, and are maintained for hours. Rhythmical motility is best obtained when the stomach contains food, however, typical results may be obtained from the stomach recently emptied. Starved animals were not studied. The phases of activity in the sphincter are such as to supplement those of the antrum, hence, the motility of these two parts may be considered as constituting a cycle of the pars pylorica.

The sequence of action in the pars pylorica is as follows: During the active phase of the preantrum there occurs a loss of tone or inhibition in the antrum as a whole. This is immediately followed by a gradual or running contraction of the antrum, the entire antrum demonstrating a sustained contraction or plateau as the final act of its positive phase. This is followed by a wave of relaxation, which, starting in the preantral region, passes over the entire antrum. The sphincter, on the other hand demonstrates a negative phase (relaxation) at the time of beginning antral contractions. Some time before the antrum enters upon its held contraction the sphincter begins to rapidly contract and reaches its maximum, usually at a time of marked relaxation of the antrum. The sphincter

then relaxes and remains quiet until a second positive phase is well initiated in the antrum. Hence, the sphincter is open during the greater part of the antral contraction and actively closed while the antrum is relaxing.

Our results along with those of Cole and Luckhardt, Phillips and Carlson demonstrate that the activities of the pyloric sphincter, at least in great part, are dependent upon the activities of the antrum. That is, the impulse to contract in the antrum during digestive processes is propagated into the sphincter, thereby causing it to contract at a time of relaxation of the antrum, and to relax because of the arrival of a wave of relaxation over the antrum. Such conditions indirectly lead to the conclusion that acid if it acts to regulate the "pylorus" must also act in a similar way upon the antrum and stomach as a whole, for, as shown above, motility of the antrum determines motility of the sphincter.

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LABORATORY METHODS

OBSERVATIONS ON THE QUANTITATIVE NATURE OF COMPLEMENT FIXATION

With Special Reference to the Clinical Application of Partial Wassermann Reactions

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BOTH laboratory workers and clinicians have long felt the need of a standard technic for Wassermann tests. The experiments which Kolmer[1] and his coworkers are now carrying on will clear up many points regarding this test that have been obscure, and settle authoritatively many questions that have been in dispute. Their work will remove some of the difficulties which have heretofore stood in the way of a standardized technic. A finally acceptable test, however, must be based not on the work and opinions of any one man or any one set of men, but on the work and opinions and experiences of many men, both laboratory workers and clinicians. The wider the range of experience from which the details of the finally proposed test shall have been gathered, the greater the probability of its general acceptance. It is desirable, therefore, that as many as possible of those interested in this matter shall contribute their opinions and observations, and it is with this in mind that the present paper is offered.

It would be an easy matter to devise a technic so conservative that it would give positive reactions only with certainly syphilitic serums. But this technic would probably fail to detect many serums containing only small amounts of fixing substances. On the other hand, it would be an easy matter to devise a technic which would detect specific fixing substances in every syphilitic serum, no matter how small the amount; but this method would probably give inhibition with some negative serums. The problem is to devise a method that will give positive reactions, even partially positive reactions, only in the presence of syphilis, and negative reactions always in the absence of syphilis.

In all cases of fully developed secondary, and, in many cases of tertiary syphilis, the serums contain so large an amount of complement fixing substances that they will always be detected by the classical test even with an indifferent technic, and in such cases there is never any variation in the findings of different workers unless some very gross error has been committed. Nor will this method, when performed with reasonable care, ever give a complete reaction with a nonsyphilitic serum. It is in those cases of primary and latent or slightly active tertiary syphilis, in which only small amounts of complement fixing substances are present in the serum, that variations occur in the results obtained with different methods and even with the same methods employed by different workers. It is for the detection and standard evaluation

of these cases, which fall in or near the zone of partial reactions, that the need for a uniform standard test is chiefly felt.

Before undertaking the modification of the Wassermann test for purposes of standardization, it should be definitely determined whether the present classical method tends to err too much on the positive side, giving partially positive reactions in negative cases; whether it tends to err too much on the negative side, giving too many negatives with syphilitic serums, or whether it errs on both sides, giving partial positive reactions sometimes in nonsyphilitics and negative in cases that should give positive reactions.

The general opinion of most clinicians and of most laboratory workers is that partial reactions, especially mildly positive reactions obtained with the present classical test, are of doubtful value. The statement "one-plus or two-plus Wassermann reactions mean nothing" has been so frequently repeated that it has come to be almost axiomatic. At most these reactions are considered only of corroborative value in cases which present indefinite history or symptoms. I have been unable to find any experimental evidence in the medical literature that would give validity to this generally accepted interpretation of partial reactions. I believe the attitude of the clinicians regarding partial reactions is largely due to the fact that the performance of the Wassermann test has been and still is often left to incompetent and insufficiently trained assistants, who commit gross technical errors. Fully as necessary as a standardized technic is a standardization of the qualifications of those who are permitted to perform the test, and provisions for enforcing recognition of these standard qualifications on all laboratories.

I am of the opinion that the classical Wassermann test, when performed with reasonable care by a skilled technician, will never give partially positive reactions in any but syphilitic cases, and this opinion is based on the following considerations:

(*a*) The originators of the Wassermann test attempted to devise the technic with a very large factor of safety against the occurrence of false positive reactions. They knew that all serums have an anticomplementary action, and that this action varies considerably with different serums. The watery extract of syphilitic liver originally used for antigen, but now almost entirely discarded, was subject to vagaries, deteriorated rapidly, and was very apt to give false, proteotropic reactions. To overcome the possibility of false positive reactions as a result of these factors, an additional unit of complement was allowed in the original Wassermann technic. This ample allowance was made because the exact extent to which the above sources of error (and perhaps some unknown sources of error) might act was not known, and it was imperative that if the test erred at all it be on the negative and not on the positive side.

It is also possible that this large extra allowance of complement was found necessary because the possibility of error due to variations in the complement content of guinea pig serums was not recognized and provided for. The preliminary titration of the original technic did not standardize the complement dose, but provided for the compensation of a deficiency of complement by the

use of an excess of amboceptor. It is now well known that this is not a valid procedure, as it does not keep the complement dose in the second part of the test at a uniform level, and may, therefore, result in false positive reactions.

Every serologist worthy of the name now guards against this possible source of error either by making a preliminary titration of complement with a standard amboceptor and corpuscle suspension, or by pooling the serums of a number of guinea pigs, or still better, by both procedures. When this precaution has been observed, keeping the complement unit at a uniform level, it will be found that for fresh or carefully preserved serums, obtained from blood withdrawn under proper conditions, the extra unit of complement allowed for anticomplementary action of serums is four or five times the amount really required for this purpose. Furthermore, the alcoholic extracts of normal organs now almost universally used as antigens in place of the original watery extracts of syphilitic livers are very stable, and if properly prepared will give ample antigenic action in doses that exhibit only negligible anticomplementary properties. The classical test, therefore, as at present performed, refined to eliminate the grosser errors of the original technic, yet retaining the device of using an additional unit of complement originally resorted to for overcoming these gross errors, tends to err altogether on the negative side.

(*b*) The difference between partial reactions and complete reactions near the partial zone is very little, if we take into consideration the amount of fixing substance present in the average serum from a case of fully developed secondary syphilis (which is considered a type of positive serum, and is recommended for use in titrating antigen and for positive controls).

In many cases of secondary syphilis, and in some cases of tertiary syphilis, the serum contains sufficient complement fixing substances so that one hundredth the usual Wassermann dose will give complete fixation with the

TABLE I

TITRATION OF AVERAGE SERUM*

Amount of positive serum	0.001	0.005	0.0075	0.01	0.05	0.1	0.2
Per cent of inhibition	5	30	60	100	100	100	100

*Inhibition estimates were made by the author's method, a description of which will be published in the near future. All work was done with one-fourth Wassermann quantities, but is reported in full Wassermann quantities.

usual dose (two units) of complement. It is seldom that, in a case of fully developed secondary syphilis, one tenth the usual dose will not give complete fixation, and it is my experience that the average is about one twentieth. In Table I is shown a titration of such an average serum. It will be seen that 0.01 c.c. (5 per cent of the usual dose) still gives complete inhibition, while 0.0075 c.c. (2.75 per cent of the usual dose) gives only 60 per cent inhibition. This indicates that a difference of 2.25 per cent of the total fixing substance found in the average serum of secondary syphilis represents the difference between a complete and a partial reaction; in other words, the difference between a surely positive and a doubtful reaction. Many of the serums in tertiary syphilis that give complete reactions are only slightly above the zone of partial reactions, that is, contain just slightly more than 5 per cent of the

amount of fixing substance found in a typical, average positive serum. If such a serum can be considered definitely specific, then a serum containing only 1 or 2 per cent less fixing substance should also be considered specific, even though it falls within the zone of partial reactions.

(*c*) If we analyze a complement titration we shall find that the general conception that various degrees of specific reaction as reported for different tests represent definitely corresponding variations in complement fixation has no basis in fact. Table II shows the result of an incubation of increasing amounts of complement with constant amounts of corpuscles and amboceptor (practically a complement titration). It will be noted that 0.5 c.c. of complement gives just complete hemolysis which, therefore, is the unit; and twice this, or 1 c.c., the dose as used in the classical test. The first trace of inhibition is seen in the tube containing 0.4 c.c. complement, which means that 0.6

TABLE II

RESULT OF AN INCUBATION OF INCREASING AMOUNTS OF COMPLEMENT WITH CONSTANT AMOUNTS OF CORPUSCLES AND AMBOCEPTOR

Amount of complement.....	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.5	0.6	0.8	1.0
Per cent of inhibition.....	90	60	30	20	10	5	2	0	0	0	0
Per cent of complement dose.....	10	15	20	25	30	35	40	50	60	80	100
Per cent of complement unit.....	20	30	40	50	60	70	80	100			

c.c. or over half of the total amount of complement employed in a test must be absorbed before a trace of inhibition is registered. The tube containing 0.2 c.c. of complement, corresponding to an absorption of 0.8 c.c. in a test, shows only 30 per cent inhibition, approximately a one-plus reaction. This means that 80 per cent of the complement dose employed in a test must be absorbed before a one plus reaction is registered. From this point on the rise is very rapid, the additional absorption of only 5 per cent more complement giving 60 per cent inhibition, and another 5 per cent giving 90 per cent inhibition. It is seen, then, that 80 per cent of the complement employed in the classical Wassermann test must be absorbed before the zone of partial reactions is reached, and the difference between a one-plus and a four-plus reaction is represented by the remaining 20 per cent of complement.

It is true, of course, that in the classical test only half of the complement is meant for specific action. It has already been shown, however, that with the refinements which have been introduced in the classical test the absorption due to anticomplementary action is only a small fraction of the additional complement unit allowed for this purpose. But even if this entire unit of complement were absorbed nonspecifically, it would still be found that 60 per cent of the complement unit left available for the specific reaction must be absorbed before a one-plus reaction is registered; that 10 per cent further fixation gives two-plus reaction and 10 per cent more brings it between a three- and four-plus reaction.

That these facts are not in accord with the great difference in clinical value generally given to partial and complete reactions is apparent. They further corroborate my contention that there is very little difference between partial reactions and complete reactions bordering on the partial zone.

(*d*) There seems to be a general misunderstanding regarding the effect on hemolysis of variations in the quantitative relations between complement and fixing substance. The usual conception is that hemolysis (or inhibition) in the indicator system varies in direct proportion to the variations in the quantitative relations of the complement and fixing substance in the first part of the test, assuming the antigen to be constant. It is thought, for instance (and theoretically this should be true), that a serum which will give just slightly less than complete inhibition with one unit of complement will give complete hemolysis with two units, because the additional unit should remain available for the indicator system and is sufficient to complete hemolysis. Practically, however, this is not true. Reference to Table III shows that a serum which gives only 75 per cent inhibition with 1 c.c. complement dilution still gives 40 per cent inhibition with 2 c.c. A serum which gives 50 per cent inhibition with 1 c.c. still gives 20 per cent with 2 c.c., and one which gives 25

TABLE III

VARIATIONS IN FIXATION WITH SPECIFIC SERUMS RESULTING FROM VARIATIONS IN COMPLEMENT QUANTITIES*

Amount of complement	0 8	1.0	1.5	2.0
Per cent inhibition with one plus serum	30	25	15	5
Per cent inhibition with two plus serum	60	50	40	20
Per cent inhibition with three plus serum	85	75	60	40

*Average findings with a number of serums.

per cent with 1 c.c. still gives 5 per cent with 2 c.c. It is apparent, then, that the relative amount of complement fixed in the presence of a constant amount of antigen and fixing substance increases as the volume of complement is increased or, vice versa, decreases as the volume is decreased. I have, furthermore, experimental evidence to show that this same law, if I may so call it, also operates in the case of nonspecific fixation. From these facts it will be seen that Wassermann tests are, in a measure, self-corrective as far as errors due to variations in complement quantities are concerned. Technicians know that, even with the greatest care, there will often be more or less variation in the complement quantities on different days. With the present conception of the quantitative nature of complement fixation, it is thought that such variations might at times bring about false positive reactions. However, in view of the real quantitative nature of complement fixation and its self-corrective action, which I have demonstrated, I believe it is safe to say that, when the usual ordinary precautions have been taken to keep the complement dose at a constant level, such differences as are unavoidable with the present technic will never be sufficient to raise a negative serum into the zone of partial reactions.

(*e*) We have, for a number of years, in our laboratory, tested all serums with a raw serum method in addition to the usual classical test. This raw serum method provides corrections of errors that may be due to variations in native complement content of raw serums, due to the presence of hemolysin homologous to that of the indicator system, and to variations in nonspecific fixation which are usually more pronounced with raw than with inactivated

serums. The method has, therefore, the advantage of increased delicacy due to the use of noninactivated serum, but is without the disadvantages usually found in other ray serum tests that tend to lead to false positive reactions. An analysis of the comparative findings which we have obtained in cases known to be syphilitic, and in presumably nonsyphilitic cases, supports my view that the classical test errs far too greatly on the side of falsely negative reactions, and that in practically all cases in which it enters the zone of partial reactions, these are specific in nature. In every case without exception in which the classical test gave a mildly positive reaction, the raw serum test gave a much more strongly positive reaction. With but few exceptions when inhibition with the classical test was as high as 50 per cent, the raw serum test gave complete inhibition. Not infrequently, in cases known to be specific, especially in cases under treatment, the classical test was completely negative when the raw serum test was partially positive and sometimes even completely positive.

(*f*) One of the reasons why the specificity of partial reactions has come to be doubted is that they have not infrequently been found in persons who give no history of syphilis and who present no symptoms of the disease. Complete reactions are also encountered in this class of individuals, but because of the misconception regarding the quantitative relation between partial and complete reactions, the latter have been considered sufficient to justify the classification of individuals on whom they have been obtained as definitely syphilitic, while the former have, erroneously enough, been considered as of no significance.

The value of a negative history seems to be overestimated. Many strongly positive and many partially positive reactions are obtained on persons giving definite symptoms of syphilis, who have no knowledge of the primary infection. Why, then, attach much significance to a negative history in the presence of partial reactions without history?

Furthermore, absence of symptoms cannot be considered a criterion of the absence of syphilis. The symptoms of syphilis, and especially tertiary syphilis, depend not so much on the character and extent of the lesions as on the location of the lesions. Lesions which in the cortical areas of the cerebrum, in the cord or iris would produce definitely recognizable symptoms, might be completely asymptomatic in the liver or spleen. In this connection the work of Warthin[2] who found evidence of syphilis in approximately 40 per cent of his necropsy material, is significant and cannot be ignored. Many of these cases presented no symptoms of syphilis during life, and gave negative Wassermann reactions. Our past conception of syphilis is probably a mistaken one. Undoubtedly the resistance of individuals to this disease varies just as much as it does to any other disease, with corresponding variations in the resultant manifestations. From the highly susceptible individual with little resistance, in whom the fulminating type develops, down to a favored few who are entirely immune, there may be every grade of susceptibility. There are probably many persons who become infected without showing any recognizable primary or secondary manifestation, and who carry the spirochetes for years in relatively unimportant tissues where they produce slowly productive lesions. The organisms may eventually become entirely dormant, or if the

resistance of the individual is lowered, as through intercurrent disease, exposure or senility, they may again become active and produce definite symptoms.

With this conception one can readily understand that partial reactions may be obtained on the blood of apparently healthy individuals, and that the mere fact that such reactions do occur cannot be considered valid evidence against their specificity.

The observations which I have presented herewith would indicate that the technic of the present classical test is extremely conservative, and provides a very wide margin of safety against the occurrence of false positive reactions. It would seem, also, that this margin of safety can be considerably narrowed without incurring the danger of false positive reactions, thereby increasing proportionately the efficiency and delicacy of the test.

Of course, if the partial reactions, which at present are looked on with suspicion, are accepted as unqualifiedly specific, that in itself will very materially increase the efficiency of the test. However, if a test can be devised that will make these partially positive reactions strongly or completely positive, a considerable advantage will be gained, because such reactions will have more conclusive value for both the physician and his patient. Furthermore, a more delicate test would give many strongly positive reactions in cases of syphilis that give completely negative reactions with the classical test. This is especially important for cases under treatment. It has, for instance, been my experience that, without a single exception, cases of syphilis under treatment have given positive reactions with raw serum tests long after the reactions with the classical test have become negative.

It is my opinion that any effort to standardize the Wassermann test will not be successful unless the technic adopted gives a very material increase in efficiency over the present method. I also believe that the highest possible degree of efficiency cannot be attained unless the method provides for testing the serum in the noninactivated state.

I realize that a great deal of prejudice exists against noninactivated or raw serum tests. This is largely due to the fact that practically all raw serum tests that have been proposed have been inexact, unscientific and subject to false positive reactions. But I am sure that a raw serum test can be devised which is exact and scientific, which will be more delicate than inactivated serum tests, and still provide an adequate factor of safety against false positive reactions.

For the present, perhaps, the ideal method would be one that includes a test with both raw and inactivated serums. This would enable us to retain our present standards of value for comparison with the raw serum method, and provide an easy stage of transition to the exclusive use of a raw serum method, should this later on be found to be justified.

The technic of the standard test should also be such that a definite, standard value can be given to partial reactions, so that there may be no confusion regarding the interpretations which are to be given them. This evaluation should be the result of careful and prolonged clinical observation, and, if possible, of postmortem study after the method of Warthin.

METHOD OF TESTING SERUMS

In closing this paper, I will briefly describe the method of testing and the method of interpretation which have been adopted in my laboratory as a result of many years of experience and observation, not because I think it ideal, for I realize that there is much room for improvement, but in the hope that it contains some suggestions that may be of value to those who have engaged in the effort to standardize the Wassermann test.

All serums are tested with the classical method, modified to avoid as far as possible the major sources of error in the original Wassermann test as follows:

(*a*) Variations in the complement content of guinea-pig serum are overcome by using pooled serums and a preliminary titration with amboceptor of known strength and standard corpuscle suspension.

(*b*) Variations in the specific fixability of guinea-pig serums are corrected by the use of pooled serums.

(*c*) Errors due to variations in the anticomplementary action of different human serums are minimized by varying the second incubation period for each serum in accordance with the hemolyzing time of the serum controls.

(*d*) Variations in the sheep hemolysin content of different human serums are corrected by the method devised by me.[3]

(*e*) A standard antigen is used, the antigenic properties of which have been determined by titration with positive serums of known strength.

(*f*) A partially positive serum of known strength is used as a positive control in the test.

In addition all serums are tested with my raw serum method,[4] which guards against the following sources of error:

(*a*) Quantitative variations in the native complement content of human serums.

(*b*) Quantitative variations of hemolysin in human serums homologous to that employed in the indicator system.

(*c*) Variations in the anticomplementary properties of different serums.

Findings are given the following interpretations:

Definitely Specific: All serums that give 100 per cent inhibition with the raw serum test, regardless of the findings with the classical test. All serums that give 50 per cent inhibition or over with the classical test, but less than 100 per cent with the raw serum test.

Probably Specific: All serums that give less than 50 per cent inhibition with the classical test, but more than 50 per cent and less than 100 per cent with the raw serum test.

Doubtful: All serums that give less than 50 per cent inhibition with the raw serum test.

Negative: All serums that give complete hemolysis with both tests.

For the practical application of these reactions, cases are grouped into four groups, as follows:

Group I: Cases that give an unmistakable history of syphilis, but with no symptoms, and who have or have not been under treatment. A single nega-

tive in these cases does not exclude syphilis. Negative reactions over a period of two years are considered evidence that the disease has been cured. Any partial reaction indicates a persistence of the disease.

Group II. (*a*) Cases that present unmistakable symptoms of syphilis. (*b*) Cases with obscure symptoms, but which have been diagnosed by the specialist (internist, neurologist or dermatologist) as syphilitic. In this group the Wassermann test is not essential, but is made for corroborative purposes or to convince the patient. Treatment is undertaken regardless of the outcome of the test.

Group III. Cases with no definite history of syphilis, and with symptoms which cannot be definitely referable to the disease, but which may nevertheless be caused by it. "Definitely Specific" reactions in these cases indicate that syphilis is present, and that the symptoms are probably, though not necessarily, caused by it.

"Probably Specific" and "Doubtful" reactions justify, in my opinion, the institution of antisyphilitic treatment, though conservatism demands that a frank diagnosis of syphilis be withheld until the results of the treatment are evident. If definite improvement results, the diagnosis is made and the case treated according to individual requirements. If no improvement results, a diagnosis of syphilis cannot be made. These reactions, then, are considered merely justification for resorting to the therapeutic test. In order to avoid unnecessary anguish of mind it is desirable, if possible, to withhold from the patient any information as to the nature of the disease suspected until the diagnosis has been confirmed by the therapeutic test. In these days of needle therapy, it should not be difficult to give intramuscular injections of mercury, or even intravenous injections of arsphenamine without divulging the true nature of the treatment.

In cases in which symptoms point to a nervous involvement, a spinal puncture should, of course, be made.

Group IV. Cases with no history of syphilis, and with no symptoms of the disease, in whom the test is made in the course of routine examinations, or for experimental, statistical or eugenic purposes. A "Definitely Specific" reaction in any of these cases means syphilis, without question. A "Probably Specific" reaction is highly suspicious. Whether such persons should be placed under treatment, or merely kept under observation, is a question to which there are two sides and to the discussion of which I cannot give space in this paper. A "Doubtful" reaction should probably be disregarded in this group.

SUMMARY

There is urgent need for a standard technic for Wassermann tests. The need of standard requirements for technicians is just as urgent.

The classical test, when properly performed by a skilled technician, tends to err altogether on the negative side. Partial reactions are always specific.

The aim should be to make the standard test more delicate than the present classical test, without sacrificing its specificity, so that a larger number of

definitely positive reactions may be obtained in cases of syphilis in which the blood contains only small amounts of fixing substances.

It is suggested that this be accomplished by testing all serums with the classical method modified to remove its major sources of error, and a raw serum test modified to remove the usual sources of error inherent in present raw serum methods.

A scheme of interpretation of partial reactions and their clinical application is given. This gives these reactions a more definite clinical value than they now have.

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COMPLEMENT VS. AMBOCEPTOR TITRATIONS IN THE WASSERMANN TEST*

By R. L. Kahn, Sc.D., Lansing, Mich.

THIS paper will endeavor to prove the desirability (1) of standardizing the time of incubation of amboceptor and complement titrations and the time of final incubation before reading the tests, to a 15 minute period and (2) of titrating both complement and amboceptor daily in the Wassermann test (guinea-pig complement, sheep-cell system).

1. The Wassermann test may be said to consist of the following two steps: First, the finding of the smallest amount of complement necessary to bring about hemolysis of a standard amount of red cells in the presence of a standard amount of amboceptor. Second, the ascertaining whether this (or a multiple of this) amount of complement will hemolyze the red cells in the presence of amboceptor, unknown serum and Wassermann antigen; or whether the latter (serum and antigen) will "fix" the complement and thereby prevent hemolysis of the cells.

Viewing the Wassermann test from this angle, it is evident that the physical factors which influence hemolysis of red cells, such as the nature and period of incubation, ought to be the same in the first step of the test as in the second. However, while most workers resort to the water-bath as the mode of incubation, they do not always employ the same period of incubation in both cases. To illustrate: one worker might employ a half-hour incubation period in his complement titration, (first step of test) and one hour incubation period before reading his tests (second step of test); while another might employ an incu-

*From the Bureau of Laboratories, Michigan Department of Health, Lansing, Michigan.

bation period of one hour in his complement titrations and approximately fifteen minutes incubation period before reading his tests.

One frequently finds still another variable element in the hemolytic system of the Wassermann test, namely, the time of incubation of amboceptor titrations. It is difficult to see why the incubation period of amboceptor titrations should vary from the incubation period of complement titrations in any given procedure; and it is no less difficult to see why the incubation periods of both of these titrations should differ from the final incubation period before reading the tests. Yet, as is illustrated by the table given below, these variations are not uncommon, Kolmer being the only worker listed, who employs a constant incubation period throughout.

TABLE I

ILLUSTRATING VARIATIONS IN THE LENGTH OF INCUBATION PERIODS OF AMBOCEPTOR AND COMPLEMENT TITRATIONS AND OF FINAL TESTS, AS EMPLOYED BY DIFFERENT WORKERS

NO.	AUTHOR	LENGTH OF INCUBATION PERIOD OF AMBOCEPTOR TITRATIONS	LENGTH OF INCUBATION PERIOD OF COMPLEMENT TITRATIONS	LENGTH OF FINAL INCUBATION PERIOD, BEFORE READING TESTS
I	Hinton[1] (Mass. State Board of Health)	1 hour	½ hour	1 hour
II	Kolmer[2]	1 hour	1 hour	1 hour
III	Koopman[3] (N. Y. City Board of Health)	1 hour	1 hour	Approx. 15 min. (Tests are read as soon as controls hemolyze
IV	Neil[4] (U. S. Public Health Service)	1 hour	½ hour	½ hour
V	Simon[5]	½ hour	———	10-15 minutes
IV	Thomas and Ivy[6]	1 hour	1 hour	1½ to 2 hours

Granting the importance of employing a standard incubation period for the hemolytic phase of the Wassermann test, it was felt that the adoption of a 15-minute period would serve the purpose best, since it would practically eliminate the old-disputed question whether to titrate complement or amboceptor in this test. Those workers who employ amboceptor instead of complement titrations in the Wassermann test, do so largely, not because amboceptor titrations render the Wassermann results more accurate, but rather because these titrations render the procedure of the test, more practical. Daily complement titrations necessarily delay the completion of the Wassermann tests, while amboceptor titrations do not and are preferred for this reason. By adopting, therefore, a 15-minute incubation period, the delay produced by complement titrations becomes comparatively insignificant, and the time objection against these titrations, is practically eliminated.

A solution to this problem was attempted by studying the amount of hemolysis produced in amboceptor and complement titrations during 15-minute, 30-minute and 1-hour incubation periods.

To begin with, the unit of new amboceptor was determined by preparing a series of dilutions of amboceptor serum and titrating each with 0.1 c.c. of a 5 per cent suspension of sheep cells and 0.1 c.c. of 1-10 pooled guinea pig complement (one-tenth quantities of

classical Wassermann). The titrations were carried out in a series of 10 tubes, in the following proportions:

Tube	1	2	3	4	5	6	7	8	9	10
Amboceptor (c.c.)	.1	.09	.08	.07	.06	.05	.04	.03	.02	.01
Complement (c.c.) (1-10)	.1	.1	.1	.1	.1	.1	.1	.1	.1	.1
Sheep-Cells (c.c.) (5%)	.1	.1	.1	.1	.1	.1	.1	.1	.1	.1
Saline (drops)	2	2	2	3	3	3	3	4	4	4

The unit was read in each case after 15 minutes incubation in the water-bath. For the sake of simplicity all the reagents in the Wassermann test are employed in 0.1 c.c. quantities. The unit aimed at, therefore, was 0.05 c.c., so that 0.1 c.c. would contain 2 units of amboceptor.

After finding the dilution of amboceptor serum which gave a unit of 0.05 c.c., the titrations were repeated daily for a week with different pooled complements in order to establish a permanent amboceptor unit.

The amboceptor unit being determined, complement units were obtained by employing pooled 1-10 complement in quantities ranging from 0.1 to 0.01 c.c., with 2 units of amboceptor and 0.1 c.c. sheep-cells, after incubation for 15 minutes in water-bath.

It was soon found that with the procedure employed in this laboratory, the difference between 15 minutes and ½ hour incubation was frequently so slight as to make it too indefinite for accurate readings and that the difference between 15 minutes and 1 hour incubation, was nothing more than one gradation in either complement or amboceptor titrations. Thus, if the complement or amboceptor unit was 0.05 at the end of 15 minutes incubation, it was 0.04 at the end of one hour incubation and if the unit was 0.04 at the end of 15 minutes it was 0.03 at the end of an hour.

By employing a 15 minute incubation period in our tests, it was a comparatively simple matter to observe the differences in these units. Thus, after reading the respective units after 15 minutes incubation, the titration racks were merely permitted to remain in the water-bath for 45 minutes longer and the units determined again. These readings were carried out daily for several months as a matter of routine, without however, keeping a record of them.

Table II based on 10 recent daily titrations, illustrates the marked constancy in the difference between 15 minutes and 1 hour incubation. The complement titrations are regularly being carried out in duplication in this laboratory because of the importance of employing a proper amount of this ingredient.

Ottenberg,[7] in discussing the incubation period of complement and amboceptor titrations, states that 1 hour is too long for practical work and 15 minutes probably too short, and suggests the adoption of a 30-minute period. According to this worker, "The 15-minute period is probably too short to allow for slight differences in the speed with which the mixtures assume the temperature of the thermostat, due to variations in the thickness of the glassware, etc." We have been employing Wassermann tubes ranging in thickness from 0.025 to 0.075 of an inch, without detecting after 15-minute incubation any variations in our complement and amboceptor titrations due to these differences in thickness. Neither have we been able to detect any other factors which tend to interfere with the correct determination of these units after this short period of incubation.*

A distinct advantage in the employment of a 15-minute incubation period,

*The writer is informed that Dr. Ottenberg has been for some time employing a 15-minute incubation period; and that Dr. Kaliski also, at the laboratory of the Mt. Sinai Hospital, New York, has been employing this short incubation period.

TABLE II

SHOWING THE EFFECT OF 15 MINUTES AS COMPARED WITH 1 HOUR INCUBATION ON THE DETERMINATION OF THE UNIT IN COMPLEMENT AND AMBOCEPTOR TITRATIONS

DATE 1920 Sept.	UNIT OF COMPLEMENT AFTER		UNIT OF AMBOCEPTOR AFTER	
	15 Minutes Incubation c.c.	1 Hour Incubation c.c.	15 Minutes Incubation c.c.	1 Hour Incubation c.c.
8	.05 .05	.04 .04	.05	.04
9	.04 .04	.03 .03	.05	.04
10	.03 .03	.02 .02	.04	.03
11	.04 .04	.03 .03	.04	.03
13	.05 .05	.04 .04	.05	.04
14	.04 .04	.03 .03	.05	.04
15	.05 .05	.04 .04	.05	.04
16	.04 .04	.03 .03	.05	.04
17	.04 .04	.03 .03	.05	.04
18	.05 .05	.04 .04	.06	.05

may be mentioned in this connection. When titrating pooled complement from 3 or 4 guinea pigs on any given day, it not infrequently happens that one of the sera is of poor complement potency and that it would be better not to use it in the mixture. With the employment of an incubation period lasting 1 hour, it is often difficult to detect the presence of the slow complement, since by the end of that time, the hemolysis is so nearly complete, due to the potent complements, that the poor complement is all covered up, so to speak. With the employment of a 15-minute incubation period, however, the finding of a slow complement in a pooled mixture is a comparatively simple matter. The series of titration tubes usually show about 90 instead of 100 per cent of hemolysis, indicating the presence of a serum which is "preventing" hemolysis. Under these conditions, each pig is titrated separately and the poor complement discarded.

In this laboratory a 15-minute incubation period is being employed for complement and amboceptor titrations, and approximately 15 minutes for the final incubation before reading the tests. Our experience with this procedure is based on 10,000 Wassermann tests. And in our opinion this short incubation period is highly desirable from both a theoretical and practical viewpoint.

2. The problem whether to titrate complement or amboceptor in the Wasser-

mann test, has recently been revived by Kolmer, Matsunami and Rule.[2] After an extensive study of this question, these investigators make, among others, this significant statement: "Adjustment of the hemolytic system by daily titration of complement has proved superior to adjustment by daily titration of hemolysin for the conduct of complement-fixation tests of syphilis." Among other workers, Ottenberg particularly has been emphasizing for the past several years the importance of daily titrations of complement in preference to amboceptor in the Wassermann test. Most workers it appears, are at present agreed on this point, except that in laboratories where a large number of tests are performed daily, complement titrations are impractical because of the delay they cause in the completion of the tests. This is especially true in those cases where 1-hour incubation periods are employed.

With the reduction of the time of incubation of the hemolytic system to 15 minutes, the element of delay practically disappears. In this laboratory with approximately 100 Wassermann tests daily, we find this element to be quite negligible. It takes from 3 to 4 minutes to set up a complement titration and with 15 minutes incubation, the complement unit is usually obtained within 20 minutes.

We do not, however, stop with this titration. We daily titrate amboceptor as well. This is done not because of the slight changes in the keeping quality of the amboceptor, but in order to insure that no less than two units of amboceptor will be employed with the complement and cell suspension of any given day. And as a result of this extra titration we have been able to avoid the occasional difficulties which come up in a Wassermann laboratory, due to an unbalanced hemolytic system.

To begin with, we do not titrate the hemolytic system in the presence of antigen. Such titrations ought to include a fixation period of the same length of time and at the same temperature as carried out in the tests. Thus, in our procedure, the complement titrations with alcoholic extract antigen, ought to be given a four-hour fixation period in the ice box, since we employ this mode of fixation in our alcoholic-antigen tests. Neither do we titrate our complement in the presence of pooled negative sera, since the sera employed would necessarily have to be that left over from the tests—in other words, comparatively old—and as is well-known, the older the serum the more complement it absorbs; it is questionable therefore, whether the complement absorption of such pooled sera would represent the amount of complement absorbed by the comparatively fresher sera employed in the test. In our opinion, the titration of complement in the presence of amboceptor and cells and the employment of two units of complement, are, so far as our present knowledge goes, highly adaptable for a routine laboratory.

To return to the amboceptor titrations, it will be recalled that the original amboceptor unit is obtained by titrating different dilutions of amboceptor-serum with a series of pooled complements diluted 1-10. For convenience, this amboceptor unit is contained in 0.05 c.c. of diluted amboceptor so that 0.1 c.c. is equivalent to two units. Now, after titrating the complement on a given day with 0.1 c.c. amboceptor as the constant and determining the proper dilution which will contain two units, it not infrequently happens that if the amboceptor

is titrated back with the two units of complement as the constant, that 0.1 c.c. of amboceptor contains less than two units. To illustrate his point, we will consider the titration of the hemolytic system of September 18th, as recorded in Table II.

1. The complement consisted of fresh pooled serum from three guinea pigs diluted 1-10.

2. The amboceptor was immune rabbit serum in a dilution of 1-2200, 0.1 c.c. of which contained two units.

3. The sheep-cells were obtained on the day before, from our own sheep, washed four times with saline and centrifuged at 1600 r. p. m. for 14 minutes, after which they were made up into a 5 per cent suspension.

4. Complement titrations were carried out with quantities ranging from 0.1 c.c. to 0.01 c.c. employing 0.1 c.c. amboceptor (2 units) and 0.1 c.c. sheep-cells, as constants. These titrations were carried out independently by two workers and the unit obtained in each case after 15 minutes incubation in water-bath, was 0.05 c.c. Therefore, 0.1 c.c. of 1-10 complement was used in the tests.

5. An amboceptor titration was then carried out several hours later (during the fixation period) and the unit after 15 minutes incubation, was found to be 0.06 instead of 0.05 c.c. If therefore, we had used 0.1 c.c. of amboceptor in our final tests, we would have employed less than two units of amboceptor.

6. In order to bring the amboceptor dilution to a point where two units will be contained in 0.1 c.c., the following proportion was resorted to:

$$2200 : 06 :: \times : .05$$
$$\times = 1833$$

Based on this finding, the amboceptor was diluted 1-1800 and 0.1 c.c. used in the final tests. In this way an unbalanced hemolytic system was avoided on that day.

The fact that the potency of amboceptor is comparatively constant for long periods has led most workers to believe that once the amboceptor unit is established it is not necessary to titrate it every day; that the daily titration of complement is sufficient. It is questionable, in our opinion, whether this reasoning is correct. It is not the titre but the keeping quality of amboceptor that is constant. The titre varies daily with the potency of the complement and with the slight changes in resistance and concentration of the sheep-cell suspension. A glance at Table II, shows a tendency for the daily amboceptor titration to run somewhat weaker than the corresponding complement titration on certain days. This is undoubtedly due to the fact that while complement titrations are generally carried out the first thing in the morning with complement just removed from the ice box, amboceptor titrations are carried out several hours later—after the Wassermann sets are undergoing fixation in the ice box or water-bath. During this interval the complement would naturally undergo slight deterioration. It is not unlikely that although the original amount of complement was two units, that by the time the amboceptor titration is carried out, $\frac{1}{8}$ to $\frac{1}{4}$ of a unit has deteriorated. If to this is added the changes in the resistance of sheep-cells, it is easy to understand, why the amboceptor titre is frequently less than two units.

To state this in another way, two units (instead of one unit) of complement are employed in the Wassermann tests in order to overcome the nonspecific binding of serum and antigen, but possibly not enough provisions are made for the natural deterioration of complement during the fixation period. We start out with two units of complement in our tests and by the time cells and amboceptor

are ready to be added, we might be dealing with 1¾ complement units instead of 2. Observations carried out in this laboratory, lead us to believe that this deterioration element is of particular importance if a given pooled complement contains a serum of low complement potency. Our findings indicate that the poorer the complement, the faster it deteriorates; and when starting out with two units of pooled complement, it is not unlikely that due to one serum of low potency, the titre of the mixture at the end of the fixation period, might be considerably less than two units. It is evident, therefore, that an amboceptor titration during the fixation period tells us whether the complement has undergone sufficient deterioration to affect the balance of the hemolytic system. If the amboceptor titration is somewhere above two units, we make no change, but if below two units, we bring it up to two units according to the procedure outlined above.

It takes no more than 20 minutes to complete an amboceptor titration. Furthermore, it is carried out during a period when Wassermann workers have ample time; no practical objections, therefore, can be raised against it. The advantage derived from these titrations, however, is quite important. The employment of a properly balanced hemolytic system from day to day, forms the basis of correct Wassermann tests. In this laboratory, aside from the employment of a 4+ and negative serum control, a doubtful control also, is included in the daily tests. A doubtful test is somewhere between a 1+ and a negative; it is a serum showing in the neighborhood of 12.5 per cent complement binding. These doubtful controls practically check from day to day, and in our opinion, this is due to the fine graduation of the hemolytic system, resulting from the combined complement and amboceptor titrations. Furthermore, we employ a cholesterinized antigen of pig's hearts with water-bath fixation and an alcoholic-extract antigen of beef heart with ice box fixation, and our tests check nearly 100 per cent. Our records show that in the last 8000 tests, only 1 in 1500 did not check.* This also we believe, is largely due to the combined complement and amboceptor titrations.

CONCLUSIONS

1. The time of incubation of amboceptor and complement titrations and the time of final incubation before reading the tests, should be the same in any given procedure; the standardization of this incubation period of 15 minutes, is highly desirable.

2. The daily titration of both complement and amboceptor in the Wassermann test, is necessary to a properly balanced hemolytic system.

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*We consider a strong positive by one method and a weak positive by the other, a check; while a strong or weak positive by one method and negative by the other, is repeated as a matter of routine.

A COMPOSITE REAGENT FOR THE DETERMINATION OF SODIUM CHLORIDE IN URINE*

By H. V. Atkinson, Chicago, Ill.

IN the determination of sodium chloride in urine, it has been found very convenient to make up the following solution:

Silver nitrate	6.67 Grams
Ferric ammonium alum	75 Grams
Nitric acid, conc.	150 c.c.
Water to	1000 c.c.

There is also needed the usual ammonium thiocyanate solution, 1 c.c. of which equals 0.01 gm. of sodium chloride, which can be made overstrength by dissolving 14 gm. of ammonium thiocyanate in 1000 c.c. of water and checking against the above reagent, 4.5 c.c. of which should equal 1 c.c. of ammonium thiocyanate solution; water is added to this solution until 4.5 c.c. of the composited reagent exactly equals 1 c.c. of the thiocyanate. The determination is made as follows:

Place 90 c.c. of the reagent in a glass stoppered 100 c.c. cylinder and add 10 c.c. of urine from a pipet. Shake and allow to stand for a few minutes, then pipet off 50 c.c. of the approximately clear solution and titrate the excess silver nitrate with the standard thiocyanate.

Calculation: Since 90 c.c. of the reagents equals 20 c.c. of the standard thiocyanate and only half of the excess silver nitrate is titrated $20 - 2$ (20 – titration) $\times 0.01 =$ gm. NaCl in 10 c.c. of urine used.

This reagent avoids measuring separately the water, nitric acid and saturated ferric ammonium alum. The precipitate settles rapidly and renders filtration unnecessary. The absolute error of measuring 90 c.c. in a cylinder is no greater than the error of measuring 20 c.c. from a pipet. The use of two extra pipets can be avoided by using a very tall, accurately graduated, 100 c.c. cylinder and thus measuring the 10 c.c. of urine on top of the 90 c.c. of standard silver solution and likewise the 50 c.c. of clear supernatant liquid for titration.

*From the Laboratory of Pharmacology, College of Medicine, University of Illinois, Chicago, Ill.

THE UTILIZATION OF THE CILIARY GANGLION FOR CLASS WORK IN THE PHYSIOLOGY AND PHARMACOLOGY OF THE EYE*

By Hugh McGuigan, Ph.D., M.D., Chicago, Ill.

IN the physiology and pharmacology of the eye, stimulation of the sympathetic nerve, as is well known, gives a marked dilation of the pupil. Constriction of the pupil is usually not demonstrated, except by varying the focus, or by the use of drugs.

Direct stimulation of the ciliary ganglion can be utilized almost as easily as stimulation of the sympathetic; and alternate stimulation of the two, makes the result of each more striking. An experiment conducted as follows is illustrative:

Anesthetize a dog, and isolate the vagosympathetic nerve; ligate and cut this. Use the central end for stimulation. Note the effect on the pupil. Now dissect in the temporal region sufficiently to expose the orbit to its depth. Find the external rectus muscle and dissect back carefully as far as possible. The ciliary ganglion is found internal to and under the external rectus, and under the superior rectus, close to the optic nerve and about an inch and one-half back of the eyeball (the distance depending on the size of the dog). The diagrams given in human anatomy locate this satisfactorily, and suffice as guides in the dissection. The ganglion is smaller than a pin head but plainly visible, and stimulation of it with a weak current leaves no doubt of its identity. It is advisable to cut the extrinsic muscles of the eye to prevent movement. It is advisable also to first dissect out the ganglion in a dead animal, to get its exact location.

We have found in most cases it is simpler to enucleate the eye with its extrinsic muscles and to work with it in warm (40° C.) saline. Such a preparation is usable for at least 15 minutes after removal. By stimulation around the cut end of the optic nerve in such a preparation, one can readily find dilator fibers, (long ciliary?) a little peripheral to this and to the temporal side the ciliary ganglion may be found, stimulation of which gives the greatest possible constriction of the pupil. We have already recorded the use of this in research work (Jour. Pharmacol., July, 1920, xv, No. 5, p. 415) and use it in class room work. The action of nicotine and other drugs can be easily demonstrated on this ganglion.

A little practice in the dissection develops adequate skill in this striking and valuable experiment. Care is necessary not to stretch or tear the post ciliary fibers (short ciliary nerves).

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EDITORIALS

Tuberculosis and Reinfection

OF GREAT interest to workers in the tuberculosis field are two recent and excellent works, "L'Infection Bacillaire et la Tuberculose," by A. Calmette, and "A Study in the Epidemiology of Tuberculosis" by Col. G. E. Bushnell. The former is written by one of the greatest French investigators in tuberculosis, the latter by one of unusual clinical and pathologic experience and a master of the literature of this disease. Many parts of these works are worthy of discussion and may be referred to in these columns later; for the present the important question of reinfection will be considered.

In 1886 Marfan[1] announced the following "law" in tuberculosis: "One almost never finds pulmonary tuberculosis, at least manifest and a progressing disease, in people who in infancy have been the subjects of scrofula (suppurative tuberculous adenitis of the neck) and who have been completely cured of this before the age of fifteen, such cure having taken place before any other focus of tuberculosis was discoverable."

In 1891 Koch[2] announced the experiments in reinoculating tuberculous guinea pigs, which led him to introduce tuberculin. Briefly, these experiments showed a more violent local tissue reaction, together with greater

tendency to healing, in second inoculations than in primary ones. Later work on the same point has shown that healing of the second ulcer occurs only if the second dose of bacilli is fairly small. In the course of some experiments on inoculation by implanting tuberculous lymph nodes, in my laboratory, we have found that the second plant results in repeated cycles of ulceration and healing, as the bacilli are set free in caseous pus by necrosis, accumulate, break through the surface, and are discharged, while the ulcer resulting from the first plant never heals. In spite of the heightened local immunity in all these experiments, the disease progresses and the animals die.

In 1907[3] Calmette published the results of experiments with cattle, and claimed that without doubt tuberculous animals were incomparably more resistent to an intravenous test inoculation than normal animals. In 1908 he addressed a letter to practicing physicians in France in an effort to ascertain the truth of Marfan's "law." He wrote, "The experiences of the laboratory show that cattle nearly always recover from a single infection (by the digestive route) if carefully isolated, whereas they rarely recover, but become actively tuberculous, if they are infected several times at short intervals, *or if they are left in prolonged contact with tuberculous animals.* It appears then that cattle, just as man, cured of former lesions, may be in some manner 'vaccinated.' It is important that we should know if child and adult immunity against tuberculosis can be established following an old light or massive infection."

The answers received all agreed that severe forms of pulmonary tuberculosis were rare in people who had received in childhood a localized tuberculous lesion.

Calmette relates many experiences of different workers bearing on the Koch phenomenon. Römer's work of 1909 is quoted, which leads to the conclusion that "Tuberculosis of reinfection invariably takes the gait of a chronic infection." Bezançon and Serbonnes[4] showed that with the guinea pig early reinfection of a tuberculous animal—from the first to the fifteenth day after the primary infection—leads to abscess formation without healing. Only after the sixteenth to the eighteenth day does the phenomenon of Koch characterized by necrosis and healing take place. These time relations, by the way, correspond pretty closely to those governing the first appearance of the positive tuberculin reaction after experimental inoculation.

Grysez and Petit-Dutaillis[5] sought to ascertain the result of repeated inhalations at varying intervals of time in guinea pigs. They learned that many infections by inhalation in close succession were infinitely less dangerous to the animal than a single infection. If the reinfections were attempted late after the first infection, the Koch phenomenon followed and voluminous necrotic lesions with widespread tissue destruction developed. Bruyant[6] injected guinea pigs with exactly eight bacilli every day and then every three days for four months. At the postmortems lesions showing extraordinary resistance were found.

From all the evidence of experiments quoted, and from the "law of Marfan" Calmette concludes that the consumptive is one who has received since childhood *successive more or less massive reinfections.*

The contradiction between Bruyant's results with guinea pigs and

Calmette's with cattle are, to my mind, explained by the supremely important factor of dosage, to which we shall return later. Apparently, small repeated infections protect, while large ones overwhelm.

Bushnell is very emphatic that reinfection from without cannot occur after a primary infection is established. "The inference is supported by analogy with the facts of other infectious diseases; in malaria there is no reinfection with organisms of the same type, in syphilis reinfection does not occur until the disease has become cured. There is no good reason why disease caused by the virulent and highly resistant tubercle bacillus should form an exception to the law that reinfections do not take place so long as the infectious agent is present." The analogy here seems to me dubious. It is certainly reasonable to suppose that in malaria and syphilis, or in typhoid, or any other truly septicemic disease, where the infecting organism is likely to be present throughout the body in stupendous numbers, any new invasion will be insignificant. It is by no means certain that the same is true of tuberculosis, where the tendency to localization is so much more pronounced, and the general immune reactions of such uncertain effectiveness. Possibly the phenomenon of staphylococcus boils may provide a closer analogy to tuberculosis. Here the body appears to submit repeatedly to a reinfection from the surface, though it is possible that there is at times also a bacteremia without lesions of the deeper tissues, a reinfection which it is able to localize, but against which it may not succeed in developing a conclusive general immunity. Granted, however, that all reasoning from analogy is perilous.

Bushnell says further, "The subject may die of an extension of his disease, but in pulmonary tuberculosis will preserve until the close of life the first degree of immunity, that is, he will develop no distant foci due to his own bacilli, and will be immune to incursions of tubercle bacilli from without." It would seem that possibly he has overlooked the frequent ischiorectal abscesses and laryngeal lesions which develop by no means always as terminal lesions.

Theobald Smith,[7] whose profound studies in tuberculosis, and whose clear vision regarding its problems, invite the greatest trust, has expressed himself very clearly on this problem of reinfection. Referring to Römer's work he says, "The resistance of the tuberculous animal to superinfection is readily broken down by slightly increased dosage, and is successful only when very minute doses come into play, as pointed out by Römer himself. Granted that Römer's inferences are correct in this, that a tuberculous focus once under way prevents the successful lodgement of the same infection in minute doses from without, we are still in the dark as to the fate of an infection of higher virulence. Römer asserts as a result of his experiments that most if not all tuberculous infection dates back to early life. This theory should be accepted with caution and reserve, although the large number of positive tuberculin tests in children give support. My own view is that a bacillus coming from without into the lungs has as good a chance, other things being equal, as one carried there from some existing internal focus. If the internal infection is massive and the fresh infection is light, the former

is more likely to produce a focus of disease than the latter. If the fresh infection is massive and the other light, the fresh infection is likely to produce disease rather than is the metastatic process."

The more we study the family history in enlightened patients, the more we realize the certainty of repeated infection in our consumptive patients. Such infections may be differently spaced, but are surely in most instances multiple, and comparable with some of the experiments—especially that with cattle—quoted in Calmette's book. The histories referred to are usually histories of family exposure and it is probably true that it is multiple—we may say cumulative infection—from without in the early years of life rather than in adult life which is important. This is indeed Bushnell's view, for in speaking of childhood infection he adds, "The especial danger of infection from tuberculous members of the family, then, lies rather in the probable large size and *frequency of the infecting doses* than in much increased probability of infection per se."

Tuberculization of the race is for the most part beneficial, as Bushnell claims, and humanity may be protected to a considerable degree by the primary infection. However, it does not as yet seem possible to be absolutely certain that reinfection from without does not occur.

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—*G. B. W.*

Treatment of Exophthalmic Goiter

RECENT literature contains some brilliant discussions and reports of most interesting experiments on the treatment of exophthalmic goiter. A definite or unquestioned remedy for all cases has not been found or accepted but the remarkable results obtained certainly carry with it promises of relief to all.

The most promising of all experiments appear to be those of O. P. Kimball and David Marine.[1] The results of their experiments show that simple goiter in man may be prevented on a large scale by the simple means of administering 2 grams of sodium iodide twice yearly, dividing this into 10 doses. They found that where no enlargement of the thyroid existed previous to the first administration of this drug none developed later whereas in a similar number of children, not so treated, 15 per cent developed simple goiter. Although this work concerns only simple goiter there is at least suggestive evidence that all forms of goiter may be prevented in the same way, as the limitations of this simple preventative have not yet been determined.

There are some who believe that exophthalmic goiter is a self limiting disease and that spontaneous cures occur at the end of 5-6 years but, even if this were true in a large percentage of cases, there would be few patients willing to trust to such luck and wait until this period is past. So then, if we attempt to calculate in percentage the cures accomplished by the different methods it must be remembered that our figures are only approximately correct.

Much experimental effort has been directed towards determining, if possible, the exact etiology, with only this much of success that we can say that we have in all cases to deal with hyperfunction of the thyroid gland as one of the causes, but whether this is due to primary changes within the gland itself or to outside stimulation from its nerve supply or from any of the other glands of internal secretory type we do not know.

That a large number of complete cures follow partial removal of the thyroid gland is a well known fact and as no recurrence of symptoms follows it seems reasonable to suppose that the cause has been found and properly dealt with. That others suffering from the same disease and treated in an identical manner either without results or with recurrence of symptoms suggests equally plainly that we have here an outside causative factor which has not been reached.

Such outside causative factors have been found in the thymus gland and the cervical sympathetic ganglia from which the thyroid receives its entire nerve supply. The intimate relation of the entire group of glands of internal secretion makes it possible that even if the symptom complex is quite constant we may have the cause located in different glands of the endocrine group in the different individuals.

Capelle reported a hyperplastic thymus gland in 95 per cent of those dying from "heart failure" during or shortly after an operation on the thyroid for exophthalmic goiter. Mattie found hyperplasia of the thymus in 74 per cent of his series of exophthalmic goiter. Kocher found hyperplastic thymus in 50 per cent of his operative cases. Although the findings vary greatly in percentage there is nevertheless definite suggestion of a close relation between the disease and the thymus. Zinorzersky treated 20 cases of exophthalmic goiter with x-ray applied only to the thymus gland and found some relief of symptoms in all cases. Waters made similar experiments and of his 16 completed cases he reports 50 per cent complete cures and 43 per cent of marked improvement. Of 9 cases which received ⅔ of the entire treatment 2 were completely cured and 5 showed marked improvement. Twenty-four others received only ⅓ of the prescribed treatment and some of these showed marked improvement.

Haberer reported a case of a man who presented himself apparently in a dying condition, cyanotic, dyspneic, covered with cold sweat and without perceptible pulse in the peripheral arteries. There was marked exophthalmus, lungs were edematous, heart and liver enlarged. One lobe of the thyroid removed one year previously, arteries on the other side tied. Haberer removed a piece of tissue from behind the manubrium 3 cm. long ½ cm. thick which resembled fat and microscopically did not seem to contain thymus

tissue. The patient began to improve and a complete cure followed in 3 months time.

Mannaberg applied x-ray to the ovaries in patients with exophthalmic goiter and in 8 cases of prolonged treatment he observed marked improvement. No complete cures were reported but there was marked decrease in the pulse rate, relief from diarrhea and improvement in the nervous symptoms.

Cannon succeeded in producing some of the symptoms of exophthalmic goiter in the cat by constant stimulation of the thyroid through the cervical sympathetic. Wilson found a pronounced and constant lesion of the cervical sympathetic ganglia in all cases of exophthalmic goiter examined and he states that there is much suggestive evidence that these changes are the result of direct bacterial infection within the ganglia. Leriche resected the sheath of the superior thyroid artery from its origin to the pole of the thyroid gland thus destroying the nerve supply to this lobe. The involved lobe of the thyroid gland decreased in size in a month's time so that there was no palpable tumor left, whereas the lobe on the other side remained enlarged as before.

These represent but a few of the many experiments reported in the literature, which, taken together tend to convince one that it is far from correct to suppose that the thyroid gland is or contains the sole cause of the disease.

The most logical way of treating Graves' disease would be by some method or agent with which one could attack all possible causes. Up to the present time the x-ray seems to have given the best results. The results of x-ray therapy in this disease vary in the hands of different workers and it appears that better success could have been obtained in many cases if heavier doses had been given. Nordentoft states that in his experience large doses are beneficial from the start and that small doses often irritate and many cause harm. Phaler of Philadelphia, who has done so much for Roentgen therapy, has outlined pretty thoroughly the technic to be used in this field and, with the present uniformity of apparatus, it should be possible to duplicate his results. Remer has shown that with certain distance, milliamperage, spark gap and time, and the modern broad focus Coolidge tube, results are uniform, regardless of the make of transformer or the age and discoloration of the tube used. It seems then that the results should be just as constant as the action of any drug. Holmes and Merrill in their discussion of this subject emphasize the fact that in order to obtain good results one must have a correct diagnosis and that attempts to reduce the size of a cystic or calcareous goiter would only end in disappointment and, probably, hypothyroidism. Cotenot reports excellent results from large doses with heavy infiltration in the typical cases. The nervous and heart symptoms show the first and greatest improvement, the goiter itself and the exophthalmus are the last to disappear.

McElfatric has summed up well the benefits of x-ray therapy in exophthalmic goiter as compared with other methods of treatment. There are no fatalities, no postoperative scars. It does not interfere with a patient's occupation, is painless and causes no inconvenience. If unsuccessful surgery

can still be performed and with less risk because of the favorable action of the rays of the thymus.

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—*C. C. B. (P. G. W.)*

Scurvy in Northern Russia

COMRIE,[1] with the British Troops in Northern Russia in 1919, saw and was able to treat a large number of cases of scurvy which appeared among the natives and prisoners at Archangel in February. The prison dietary which was in operation for more than a year, was as follows:

Flour or biscuit	11 ounces
Rice, oatmeal, peas or beans	7¼ "
Frozen or tinned meat, or salt-herring	7¼ "
Bacon or pork	1¾ "
Tea	¼ "
Sugar	1 "
Salt	¾ "
Lime juice (preserved)	½ "

It will be evident that the above diet was altogether too limited, being deficient not only in proteins, but in carbohydrates and vegetables. The preserved lime juice had no effect in preventing the development of scurvy; possibly it might have been of some value in furnishing a small amount of alkali. All the meats were boiled for three hours. After men had been living on the above given diet for between four and five months they developed scurvy. The development of this disease was probably enhanced by the crowded condition of the prisons, the bad surroundings, and the darkness of the long Arctic winter. Besides, there were other diseases, such as typhus, typhoid, influenza, and pneumonia, which possibly had some influence upon the rapidity with which the scurvy developed. As a rule, the first sign was a purpuric rash on the legs. As this came out the pa-

[1]Edinburgh Medical Journal, April, 1920.

tient complained of mental depression, loss of energy, and physical weakness. Soon the gums were swollen and bleeding. The ankles became edematous and complaint was made of pain in various parts of the body, especially in the head, chest, or legs. About eighty per cent of the cases showed the gums tender, swollen, often ulcerated, and frequently bleeding. In many there was an extensive pyorrhea, the teeth being loose and surrounded by pockets of pus. About eighty-six per cent showed well marked hemorrhages and these were at points on the body most frequently subjected to pressure, like the trochanter, elbow, shoulder, and in localities where blows had been received. In about fifty per cent of the cases hemorrhage was found deep in the muscles, usually in the legs, accompanied by tenderness on pressure, with pain. They caused marked limitation in the movements of the limbs. It was somewhat difficult to distinguish hemorrhages into the joints from those about the joints. The joints were frequently swollen, tender, and constantly kept, so far as possible, immobile. These joint affections were in evidence not only among the prisoners, but among the natives in civil hospitals. During recovery the hemorrhages into the muscles were absorbed with striking rapidity, large black and hardened areas of from four to five inches in diameter disappearing completely in two or three weeks. Hemorrhages into internal organs also occurred and were in evidence in those cases which came to autopsy. In two cases there was hemorrhage from the bowel and in two others from the urinary passages during life. In all cases the heart beat was feeble and in many functional murmurs were easily detected. At autopsy the cardiac muscle showed a high degree of brown atrophy with great reduction in the size of the ventricles. In some cases sudden death resulted from effusions in the pleural cavities. Anemia marked the more advanced cases. It had the characteristics of a secondary anemia with lymphocytosis. It was rather surprising to find that the coagulation time of the blood was not appreciably altered and that there was no tendency to hemorrhage when superficial wounds were inflicted. There was a slight diminution in the alkalinity of the blood. The urine showed but little or no abnormality, albuminuria being observed only five times. In four cases out of fifty the urine was alkaline.

There was no difficulty in making a diagnosis of the advanced cases, but the disease was not recognized in its incipiency. In early cases there might be nothing more than a rash on the legs with more or less edema, accompanied usually by mental depression. Cases at this stage were diagnosed under widely different heads.

Under the weather conditions existing in northern Russia it was found that scurvy was easily prevented by issuing a ration of germinated peas or beans. For germination the dry peas or beans are steeped in water for from one to two days until the embryonic root begins to sprout. They are then spread on one damp cloth and covered by another and kept in this state at proper temperature until the sprouts become about half an inch long. These germinated peas are lightly boiled with milk or water not exceeding half an hour. Beans do not germinate so easily, and therefore are less suitable for the army ration in cold countries than peas. Lemons or fresh lime juice are of value, but the preserved lime juice is without value.

For experimental purposes Comrie took forty-eight cases having the disease

with about the same degree of severity and divided them into six groups of eight each, indicated by the letters A, B, C, D, E, and F. These were segregated from one another and kept under guard. All of these men had a general diet, which consisted of bread, twelve ounces; oatmeal, two ounces; fat, one ounce; frozen meat, ten ounces, boiled for three hours; milk, two pints, boiled for one and one half hours; and ungerminated peas or beans, eight ounces, boiled for three hours. For the purpose of the test, to this common diet there was added to that of group A the juice squeezed from four ounces of fresh lemon; to group B eight ounces of germinated peas lightly boiled instead of the same quantity of ungerminated peas; group C eight ounces of germinated instead of ungerminated beans; group D ten ounces of fresh underdone meat instead of well frozen meat; group E eight ounces of tinned fruit; group F two pints of unboiled soured milk, replacing the well-boiled milk of the other groups.

After six weeks well marked improvement occurred in all six groups. Judged by the general well being and more precisely by the increase that had occurred in body weight the groups improved as follows: Group F (soured milk) showed most marked improvement, having added over fourteen per cent to the original body weight; group D (fresh meat) and group A (lemon juice) came next with an addition of between ten and eleven per cent; group B (germinated peas) seven per cent, and groups E (tinned fruit) and C (germinated beans) from six to seven per cent. The germinated beans had a tendency to cause diarrhea.

The local lesions in the mouth were washed with alum water or hydrogen peroxide, while the gums were painted with salicylate of soda dissolved in alcohol or with tincture of iodin. In order to hasten the absorption of the hemorrhages the areas were painted with tincture of iodin; then applications of hot water, combined with massage, were used. The contractures of the limbs required prolonged treatment by massage with oil inunction. Such tonics as iron, arsenic, and strychnin were found to be unnecessary. It will be seen from this that cases of scurvy recover with great rapidity with proper diet and under favorable circumstances. In the majority of instances the patients were normal practically within a month, with the exception that all the hemorrhages had not been absorbed and the contractures had not been relieved.

—*V. C. V.*

The Effects of Deficient Dietaries on Monkeys

McCARRISON[1] at Coonoor, India, captured a lot of monkeys from the local jungles, divided them into groups and placed them on different diets, with the following results:

(1) An exclusive diet of autoclaved rice—that is to say, one deficient in suitable protein, in fat, in accessory food factors of all three classes, and excessively rich in starch. Ten monkeys were fed to the point of death on this diet.

(2) A diet of autoclaved rice and butter—that is to say, one deficient in

[1]British Medical Journal, February 21, 1920.

suitable protein, in accessory food factors of the B and C classes and excessively rich in starch as well as fat. Four monkeys were fed on this diet to the point of death.

(3) A diet of autoclaved food—rice, wheaten bread, milk and ground nuts—to which a small ration of fresh onion was added; that is to say, a diet deficient in accessory food factors of the A and B classes. Six monkeys were fed to the point of death on this diet.

(4) A diet of autoclaved food—rice, wheaten bread, milk and ground nuts—to which fresh onion and fresh butter were added; that is to say, a diet deficient only in accessory food factors of the B class and excessively rich in fats. Five monkeys were fed chiefly on this diet to the point of death.

(5) Nine monkeys fed on wheaten bread, plantains, milk, fresh onions and ground nuts, acted as controls.

It is worthy of note that the animals which received rice plus butter lost weight faster and died quicker than those that received rice only. One of the most interesting points brought out in this investigation is that those animals kept on a deficient diet developed dysentery. For a day or two the stools were diarrheal and then they became dysenteric, being followed with mucus streaked with blood. Finally, in many animals for a time the stools consisted solely of blood and mucus. In two cases the dysentery was not preceded by diarrhea. As a rule, the animals survived the onset of the dysentery for only a few days, from four to seven. The symptoms were those of amebic dysentery and amebae were found in the stools. In order to determine whether these monkeys were carriers of amebae, before the experiment was begun the feces of eight healthy animals were examined and a few amebae were found in only one of these. During the greater part of the experiment the control monkeys remained free from gastrointestinal disturbances of any kind. Towards the close, however, seven developed jaundice thought to be due to a too generous provision of monkey-nuts with lack of exercise. Under a more meager diet of bread and milk to which a pinch of Epsom salts was added after a few days the jaundice cleared up. In no control monkey did either diarrhea or dysentery occur. This is a matter of great importance. One would conclude from these investigations that in many instances at least, there are two factors in the causation of amebic dysentery. One is the parasite and the other is the food. The author calls attention to the fact that it is a common practice, especially in India, for people, either through the physician's advice or on their own initiative, to confine themselves to bread and butter and milk puddings when they have any form of dysentery. The author states:

"It is my experience in India that the dietetic history of European sufferers from chronic colitis, and all those suffering from chronic gastrointestinal disorder, commonly reveals the fact that their food does not contain the requisite proteins or the due proportion of starch, fats, salts, water, and vitamines. This one cannot 'digest' vegetables, fruit, or meat, or 'never touches them in India;' that one can 'carry on only on farinaceous food.' Thus the form of diet they commonly adopt is often that most calculated to promote the very disorder from which they seek relief. These experiments show that the cardinal effects of deficient and ill-balanced dietaries in monkeys are gastrointestinal disorder, dilatation of the stomach, gastritis, and colitis. They are likely to be the same in man.

It did not surprise me, therefore, to find that a patient who consulted me recently, and who for ten years had subsisted mainly on milk puddings, had a dilated stomach, air locks in the small bowel which caused her great discomfort, delay in the passage of the intestinal contents, colitis, tenderness in the caecal region, and an inefficient pancreas with glycosuria. The results of these experiments have helped me to vizualize the changes which are likely to be occurring in the gastrointestinal tract in such a chronic invalid. I desire, therefore, to emphasize the importance in practice of a study of the dietetic history in such cases, believing as I now do that bacterial agencies are often but weeds which flourish in soil made ready for them by dietetic defects, and believing also that in the fuller comprehension of the science of dietetics we shall understand more perfectly the beginning of disease and its therapy."

Postmortem examination showed practically all the lesions characteristic of acute amebic dysentery. There were found congestion and inflammation of the mucous membrane of small intestines, with frequent subserous ecchymoses. Necrotic changes in the mucous membrane of the stomach were found and ecchymoses were frequently present at its pyloric end. In one case an ulcer was found at the pylorus. There were areas of congestion, more or less marked throughout the small intestine. In the large intestine there was marked inflammatory change, sometimes extending throughout the length of the large bowel, but more marked in the lower six inches. In rare instances the colitis was limited to areas of the transverse colon. In these areas there was pronounced ballooning of the intestinal walls.

—*V. C. V.*

From the American Society for the Control of Cancer, New York City

FOLLOWING is a statement made by Dr. Harvey R. Gaylord, one of the Directors of this Society and Director of the State Institute for the Study of Malignant Disease, Buffalo, New York:

"The people of the State of New York will want to receive a statement on the stewardship of the purchase of 2¼ grams of radium, for which $225,000 was appropriated by the State, and announcement of which was made by Governor Smith a few days ago.

"I am very glad to take this opportunity both in the name of the Institute for the Study of Malignant Disease, the State and the American Society for the Control of Cancer which supported this purchase to say these words:

"The experiment in state ownership of a therapeutic agent, as exemplified in the purchase of this radium for social utility will have a far reaching effect. This is a development of state medicine to which no one can object and Governor Smith deserves the thanks of the State for what he did.

"Any citizen of the United States may avail himself gratuitously after October 15th of treatment with the 2¼ grams valued at $225,000, recently purchased by New York State, and the first gram of which was delivered by the Radio Chemical Corporation of New York last week. Preference, however, will be given to citizens of New York State.

"The first gram is now in the vaults of the Institute at Buffalo and the appliances necessary for its use in the treatment of cancer are now in course of construction. The engagement of a competent physicist to work with this radium is also announced. The radium we are using is an American product, mined in Colorado, brought 2900 miles across the continent in the form of 125 tons of carnotite ore to the extraction plant at Orange, N. J., where it was reduced by fractional crystallization to its present state.

"The first purchase of radium by any State marks a step in the health activities of an American Commonwealth. Up to the present we have had no therapeutic agents so expensive that they could not be afforded by the average practitioner. In the case of radium that condition arises. The unit for efficient use costs not less than $12,000 and represents 100 mgs. A gram is worth $120,000. The greater the quantity in an installation the more efficient it is, and the less it costs per treatment. New York State has met this condition by purchasing an amount available for all its citizens.

The value of radium has already arrived at a stage where states, and if necessary the government, should make radium available for cancer treatment gratuitously and beyond the realm of financial limitations. The advent of radium as a therapeutic measure is the most important forward step in the treatment of cancer.

"It is not surprising that when radium first made its appearance over-optimistic claims for its use and hope of its utility should have occurred. But that time is now past. Radium has been made available in smaller and larger amounts to all of the important centers of cancer research in this country, with the result that not alone has new knowledge of this agent been greatly advanced but the technic of its use, as well as its limitations, have been more definitely defined. The last six years have marked steady progress in its application, and means of more scientifically and more efficaciously employing it have been developed.

"The State Institute, as a result of carefully controlled scientific experiment in its hospital, felt that the time had come when the State of New York should logically provide an adequate amount of radium for the Institute on the basis that its value is so definitely demonstrated that it should be made available without cost to the citizens of the State and that the opportunities for research should now be extended along practical lines. The State Institute has had since 1914 an amount of radium sufficient for scientific study. Private philanthropy has given the Memorial Hospital in New York City a large amount of radium for scientific investigation and practical application for the past four years. The Cancer Research Commission of Harvard University has also had an adequate working supply. The advances made in these and other quarters has steadily strengthened the confidence in the use of this agent and all of these centers are now seeking means to increase their supply.

"The State of New York which in 1898 took the lead by founding the first modern State Cancer Research Institute in this country should properly be made the first state to appropriate the necessary funds for the purchase of a sufficient amount of radium for the use of its citizens, having available for this purpose a center of cancer knowledge and fully equipped scientific re-

search laboratories where its use can be made immediately effective, and from which scientific progress can be confidently anticipated.

"The usefulness of radium in the treatment of neoplasms is still in its infancy, but there are already certain kinds of cancer in which its use offers advantages and the results obtained are an improvement upon any means we have heretofore possessed. It must, however, be remembered that our main reliance in the treatment of cancer is surgery, but radium in combination with surgery, frequently greatly improves the prospective cure.

"The scientific development of the last two years in the use of radium, largely through the work of Professor William Duane of Harvard University, made available a means of using radium which has immensely strengthened its usefulness. This method is the use of the emanation of radium in place of the application of radium itself. This method is only available when you have at least one gram.

"Cancer today is one of the most important diseases in the United States. It increases 25 per cent every ten years. In the United States 90,000 deaths occur yearly from it, being of equal importance to tuberculosis. In New York State about 8000 deaths occur yearly.

"The purchase of the radium has other significance than merely its use for the treatment of cancer. It gives an opportunity for research and its use under scientific conditions is sure to increase our knowledge of cancer. While surgery still remains our main reliance in the fight against cancer we can only hope greatly to improve the results of surgery by bringing the patient to surgical treatment at the earliest possible moment. This can only be accomplished by the diffusion of knowledge among the laity of the first beginnings of cancer. It is with such work as this, that the Society for the Control of Cancer has particularly charged itself. It is felt by the Society that the advent of an alternative will overcome the reluctance of many cases to present themselves to their physicians. The Society represents 900 physicians and laymen and looks with great interest at the purchase and congratulates New York upon the step it has taken.

"The purchase of this radium by an American Commonwealth from an American Company which has mined its ore in the State of Colorado, will bring still further to the fore the preeminence of America in the treatment of cancer. Buffalo will become a radium center. While Europe, through Madam Curie, first made the precious element known to the world, the United States has developed both the ore, its extraction and its use as a therapeutic agent. It is today in the forefront of treatment of cancer. This purchase may have a tremendous effect upon further progress in this direction."